MEDICAL PROCEEDINGS

MEDIESE BYDRAES

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REDAKSIONEEL · EDITORIAL

DIE SEISOEN VAN ANTIBIOTIESE VRUGBAARHEID

PAROMISIEN*: 'N DUBBELWERKENDE ANTIBIOTICUM

SEASON OF ANTIBIOTIC FRUITFULNESS

PAROMOMYCIN*: A DOUBLE-DUTY ANTIBIOTIC

'Season of antibiotic fruitfulness,
Close bosom-friend of the maturing earth;
Conspiring with her how to load and bless
With potency all saprophytes of worth.'

On Looking into Keats' Unpublished Odes.

Met die geduld en vlytigheid wat alle moderne antibiotiese navorsingswerk kenmerk, is meer as 2,000 grondmonsters ondersoek voordat 'n wortel van Guinee-gras, afkomstig van 'n beesplaas naby Miranda, Kolombië, Suid-Amerika, 'n saprofiet, geïdentifiseer as *Streptomyces rimosus forma paramomycinus*, opgelewer het. Hierdie organisme verskaf 'n 'misien', die terapeutiese gebruike waarvan bepaal word deur die feit dat dit nie uit die spysverteringskanaal geabsorbeer word nadat dit ingeneem is nie. Die aktiwiteitspektrum daarvan is anti-amebies sowel as bakteriebestrydend.

Dit skyn asof sy anti-amebiese krag heeltemal onafhanklik van sy anti-bakteriese krag staan. Dit het 'n regstreekse amebe-vernietigende effek, en hierdie eienskap word onregstreeks aangevul deur die teëwerking van bakterieë wat nodig vir die ondersteuning van amebe is.

With the patience and industry which characterize modern antibiotic research, over 2,000 soil samples were screened before a root of Guinea Grass from a ranch near Miranda, Colombia, South America, yielded a saprophyte identified as *Streptomyces rimosus forma paromomycinus*. This organism yielded a 'mycin' the therapeutic applications of which are determined by the fact that it is not absorbed from the alimentary tract when ingested. Its spectrum of activity is antiamoebic as well as antibacterial.

Its antiamoebic potency appears to be independent of its antibacterial properties. It is directly amoebicidal and supplements this property indirectly through inhibition of bacteria necessary for the support of the amoeba.

In intestinal amoebiasis it is active in the treatment of acute cases as well as chronic cyst carriers. This has been demonstrated in an

* Bemark in Suid-Afrika as Humatin (Parke, Davis).

*Marketed in South Africa as Humatin (Parke Davis).

Wat ingewandsamebiase betref, is dit aktief in die behandeling van akute gevalle sowel as chroniese siste-draers. Dit is reeds gedemonstreer in 'n indrukwekkende reeks ondersoeke wat Afrika, Asië en die Amerikas ingesluit het.

In die geval van ingewandsinfeksies het intensiewe studies die waarde daarvan bewys by die behandeling van paratifoïed-toestande, Salmonella-draers en akute disenterieë en diarrees veroorsaak deur Salmonella, Shigella en *E. coli,* sowel as diarrees te wyte aan gemengde en ongediagnoseerde nie-spesifieke infeksies. Profilakties is dit gebruik vir die voorkoming van die verspreiding van ingewandsinfeksies, en aanspraak word daarop gemaak dat dit van spesiale waarde vir die beskerming van pasgeborenes is.

Die feit dat dit nie uit die derm geabsorbeer word nie, het uitgeloop op die doeltreffende gebruik daarvan vir die verlaging van die bakteriese inhoud van die derm voor 'n operasie.

Die produksie van toksiese stikstofhoudende stowwe binne die derm ten gevolge van bakteriese ensieme bemoeilik die behandeling van lewerkoma. Paromomisien onderdruk ammoniavormende bakterieë, en neem dus sy plek in as 'n antibioticum vir die behandeling van lewerkoma. Dit het geen steurende effek op die gelyktydige toediening van die proteïene wat vir lewerselherstel nodig is nie.

So te sê geen verslae is ontvang oor newe-effekte wat op die gebruik van hierdie antibioticum volg nie. Aangesien sy werkingsplek binne die derm is, is dit begryplik dat sommige navorsingswerkers 'n vermeerdering in die aantal daaglikse ontlastings gerapporteer het. Die ontlasting word egter nooit waterig nie, dit gaan nie van krampe, mislikheid of braking vergesel nie, en ná behandeling keer die ingewandspatroon gou na normaal terug.

Die volle spektrum van die chemoterapeutiese effek van hierdie antibioticum word nog ondersoek. Dit skyn asof dit aktief is teen etlike parasietsoorte benewens *E. Histolytica.* Dit is derhalwe waarskynlik dat verdere rapporte oor hierdie interessante nuwe antibioticum eersdaags beskikbaar sal wees.

'N PENISILLINASE-WEERSTANDSKRAGTIGE PENISILLIEN

DIMETOKSIFENISILLIEN*

'n Feitlik ononderbroke stroom van berigte oor belangrike vorderings van groot terapeutiese betekenis word deesdae ontvang. Teen die einde van verlede jaar† het ons 'n dramatiese deurbraak aan die sintetiese penisillienfront aangekondig. Toe ons 'n beskrywing van die ontdekking en die eienskappe van 'n nuwe mondelinge sintetiese penisillien verstrek het,

* Bemark in Suid-Afrika as *Celbenin* (Petersen Ltd.) en *Staphcillin* (Bristol Laboratories).

† Med. Bydraes, 14 November 1959, bl. 480.

impressive series of investigations including Africa, Asia and the Americas.

In enteric infections intensive studies have demonstrated its value in the treatment of paratyphoid carrier states, Salmonella carriers and acute dysenteries and diarrhoeas caused by Salmonella, Shigella and *E. coli* as well as diarrhoeas due to mixed and undiagnosed non-specific infections. Prophylactically it has been used to prevent spread of enteric infections, being claimed to be of special value in protecting the newborn.

Its unabsorbability from the bowel has led to its effective use in lowering the bacterial content of the bowel before surgery.

The production of toxic nitrogenous substances within the gut as a result of bacterial enzymes complicates the management of hepatic coma. Paromomycin suppresses ammonia-forming bacteria and thus takes its place as an antibiotic in the treatment of hepatic coma. It does not interfere with the concurrent administration of proteins essential for liver cell recovery.

There have been almost no reports of side effects with this antibiotic. As its locus of action is within the gut it is understandable that some investigators have reported an increase in the number of daily stools. These, however, never actually became watery, were unassociated with cramps, nausea or vomiting and the bowel pattern rapidly returned to normal after treatment.

The full spectrum of the chemotherapeutic effect of this antibiotic is still being investigated. It appears active against several parasites other than *E. histolytica.* It is likely, therefore, that further reports will become available about this interesting new antibiotic.

A PENICILLINASE-RESISTANT PENICILLIN

DIMETHOXYPHENICILLIN*

Important advances of great therapeutic significance continue to be reported almost unabated. Towards the end of last year† we announced a dramatic break-through on the synthetic penicillin front. In outlining the discoveries and the properties of a new oral synthetic penicillin we indicated that the isolation of the penicillin nucleus created a unique

* Marketed in South Africa as *Celbenin* (Petersen Ltd.) and *Staphcillin* (Bristol Laboratories).

† Med. Proc., 14 November 1959, p. 480.

het ons gesê dat die afsondering van die penisillienkern 'n unieke toestand skep waar 'n bykans onbeperkte aantal nuwe penisilliene in die laboratorium geformuleer kan word *inter alia* deur die byvoeging van verskillende syketтings. Ons het dan ook voorspel dat verdere merkwaardige ontwikkelinge eerlank aan hierdie front verwag kan word. In daardie sin is dit derhalwe nie verbasend om te verneem van 'n verdere byvoeging tot die penisilliene nie. Die rol hiervan bly voorlopig in die eerste en vernaamste plaas beperk tot die behandeling van stafilokok-infeksies wat weerstand teen die konvensionele penisilliene bied. Daar is tans met 'n redelike mate van sekerheid vasgestel dat stafilokokke weerstand teen penisillien bied omdat hulle 'n ensiem-penisillinase produseer wat die penisillien inaktiveer. Daar word beweer dat die jongste wysiging van die penisillienmolekule geensins deur die ensiem geaffekteer word nie, en dat dit sy hoë aktiwiteit behou.

Berigte gepubliseer in die Lancet‡ dui darop dat penisillinase, verkry van *Bacillus cereus,* die nuwe penisillien stadig inaktiveer, hoewel dit nie sy doeltreffendheid teen alle stafilokokke verminder nie.

Alles in ag genome kan ons derhalwe sê dat 'n kragtige nuwe penisillien geskep is. Dit werk met behulp van 'n meganisme wat verskil van dié wat die eienskappe van die konvensionele penisilliene bepaal.

Op die oomblik is dit nie doeltreffend as dit per mond toegedien word nie. Dit moet al om die 4–6 uur binnespiers ingespuit word. Die bestek van die nuwe penisillien word baie knap opgesom deur die *Lancet* wat verklaar dat hoewel dit op die oomblik hoofsaaklik van waarde is weens sy aktiwiteit teen penisillinase-produserende stafilokokke, dit ook aktief teen baie ander piogeniese Gram-positiewe kokke, insluitende beta-hemolitiese streptokokke, *Streptococcus viridans,* en die pneumokokke is. Onder die Gram-negatiewe mikro-organismes is dit middelmatig aktief teen die meningokokke maar inaktief teen die Gram-negatiewe basille, selfs teen 'n soort *Salmonella typhi* wat betreklik gevoelig vir penisillien-G was. Dis teleurstellend dat 'n belangrike groep, insluitende nie alleen die salmonellas nie, maar ook die kolivorms, die shigellas, *Pseudomonas pyocyanea,* en Proteus spp., dus buite sy aktiwiteitsbestek val.'

As die nuwe penisillien rasioneel aangewend word wanneer daar behoorlike indikasies vir die gebruik daarvan bestaan, behoort dit een van die grootste bakteriese gevare wat in die na-oorlogse jare 'n werklike bedreiging vir ons geword het, uit die weg te ruim. Soos die *Lancet* daarop wys, moet die nuwe antibioticum ,op so 'n manier gebruik word dat ons nie eenvoudig Gram-negatiewe basille in die plek van Gram-positiewe kokke stel, en die pes toelaat om soos tevore voort te woeker nie.'

‡ Redaksioneel (1960): Lancet, **2**, 585.

situation whereby an almost unlimited number of new penicillins could be created in the laboratory *inter alia* by the addition of varying side-chains. We predicted that further remarkable developments could be expected on this front in the near future. In that sense, therefore, it is not surprising to learn of yet another addition to the penicillins. This finds its role, for the time being, pre-eminently in the treatment of staphylococcal infections resistant to the conventional penicillins. It has by now been reasonably well-established that staphylococci are resistant to penicillin because they produce an enzyme penicillinase with inactivates penicillin. The latest modification of the penicillin molecule is claimed to be wholly unaffected by the enzyme but it nevertheless retains its high activity.

Reports published in the Lancet‡ indicate that penicillinase extracted from *Bacillus cereus* slowly inactivates the new penicillin, although this does not lessen its efficacy against all staphylococci.

All in all, therefore, a potent new penicillin has been created. It acts through a different mechanism from that which determines the properties of the conventional penicillins.

At present it is not effective when given by mouth and must be administered intramuscularly every 4–6 hours. The scope of the new penicillin has been very admirably summarized in the Lancet‡ which noted that although it is at present chiefly valued for its activity against penicillinase-producing staphylococci, it 'is active also against many other pyogenic gram-positive cocci including beta-haemolytic streptococci, *Streptococcus viridans,* and the pneumococcus. Among the gram-negative microorganisms, (it) is moderately active against the meningococcus but inactive against the gram-negative bacilli, even against a strain of *Salmonella typhi* which was relatively sensitive to penicillin G. Disappointingly, this excludes from its range of activity an important group including not only the salmonellas but also the coliforms, the shigellas, *Pseudomonas pyocyanea,* and Proteus spp.'

If the new penicillin is used rationally when it is properly indicated, it should eliminate one of the greatest bacterial hazards which has faced us as a veritable menace in the post-war years. As the *Lancet* points out, the new antibiotic must be used 'in such a way that we do not simply substitute gram-negative bacilli for gram-positive cocci and allow the plague to rage as before.'

‡ Editorial (1960): Lancet, **2**. 585.

CYTOSTATICS IN NEOPLASIA

PERSONAL EXPERIENCES DURING TRIALS FOR ONE YEAR *

A number of preparations were tested by systematic clinical trial during previous years; 5 of them were followed up more closely on 86 patients. Two preparations, Endoxan and 5-fluor-uracil, were of particular interest because of their outstanding promise. Hormone treatment is not discussed.

Because of the experimental character of this trial, only such patients were chosen who had received all other available methods of treatment, or could no longer be considered for this. When possible, patients received X-ray treatment before chemotherapy, as irradiation could possibly make neoplasm more sensitive to chemotherapy. Most of the patients therefore showed advanced states of cancer, already operated on or inoperable, already irradiated or incapable of receiving such treatment, with metastases and complications.

Actinomycin C was tried on 11 patients; one (carcinoma of the colon) yielded remarkable results in combination with irradiation. The remaining patients did not show encouraging results. With E 39, used on 7 patients, no notable results were obtained; 8 patients were treated with carcinophyllin, but no noteworthy remissions were observed.

The largest group was treated with Endoxan (41) and 5-fluor-uracil (21).

Endoxan, a cyclophosphamide, is inactive *in vitro* but very active *in vivo*. Clinical tests indicate its suitability whereas the toxicity is sufficiently low to justify its clinical use.

The following dosage schedule was adhered to:

Intravenous: 100 mg. the first day, then 200 mg. increasing to 300, 400 and even 500 mg. daily. Large doses were divided into 2 single injections or given by infusion. The dose was then reduced to 200 mg. daily.

Per Os: 100–200 mg. per day for maintenance therapy.

The effect was judged on the patient, on the bone marrow and on the tumour tissue. Erythrocytes and thrombocytes were unaffected for a long time. The leucocyte count, which drops, is used as a criterion. The total count may be depressed to 1,500 per c.mm. and is rapidly restored when administration is diminished or interrupted.

Total dosage and results, divided into subjective and objective (clinical) findings are demonstrated in a Table which includes 21 European and 20 Bantu patients. Hodgkin (2), reticulum cell sarcoma (2), mammary carcinoma with metastases (4), subacute myeloid leukaemia (3) and chronic lymphatic leukaemia (5) responded particularly well.

In gastric carcinoma (2), myeloma (1), malignant hepatoma (4), carcinoma of the bronchus (4) and lymphosarcoma (1), results did not seem to be very encouraging.

Other growths, e.g. carcinoma of the rectum, colon, face, cervix, etc. showed only slight improvement or remained unchanged.

Total dosage varied from 1,200 mg. to 52,500 mg. and the duration of treatment from 6 to 320 days. Maximum daily average doses: 670 mg. (malignant hepatoma); 430 mg. (subacute myeloid leukaemia), 333 mg. (hodgkin). Minimum daily average doses: 53 mg. (mammary carcinoma with metastases); 76 mg. (carcinoma of the bronchus).

However, there was not necessarily a direct relation to total dosage, maximum or minimum daily doses and duration of treatment to positive or negative clinical results.

5-fluor-uracil is a fluorine-containing pyrimidine. It inhibits growth of tumour cells *in vitro*. The results are summarized in a Table (21 patients, 9 European, 12 Bantu).

Carcinoma of the colon with metastases (3) and gastric carcinoma with and without metastases (2) responded well. In malignant hepatoma (11) survival time after diagnosis was significantly increased.

(Comparative figures from the Pretoria General Hospital:
Symptomatic treatment 1–81 days.
On Endoxan 14–64 days.
On 5-flour-uracil 23–137 days).

Carcinoma of the vulva, pancreas, pharynx, remained unchanged or did not respond.

The duration of treatment varied from 8 to 124 days.

Daily maximum average doses: 594 mg. (malignant hepatoma); 357 mg. (carcinoma of the vulva); 238 mg. (carcinoma of the colon).

Daily minimum average doses 82 mg. (carcinoma of the pharynx); 90 mg. (gastric carcinoma); 110 mg. malignant hepatoma). Here again, there was no direct relation to total dosage, duration of treatment, etc. to the clinical results obtained.

* Summary of a paper by Prof. H. W. Snyman and Dr. G. Falkson (Department of Internal Medicine, University of Pretoria, Pretoria), from *Geneeskunde*, February 1960, pp. 40–47.

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THE ORAL POLIO VACCINE CAMPAIGN

It is a matter for considerable regret that the authorities embarked upon a campaign to immunize the community with an oral polio vaccine without first briefing the medical profession on the implications of this step, particularly as the procedure is one which has not yet been adopted in the U.K. or in the U.S.A. When a public authority embarks upon an immunological adventure of this kind, it should have a very clear appreciation of the repercussions of its policy and the obligations it must assume to advise medical practitioners in a timely fashion of the scientific implications of the programme. Unless this is done medical practitioners will be in no position to give consistent or even accurate answers to parents who consult them about the advisability of allowing their children to receive the oral vaccine.

The somewhat belated information which reached the profession has indicated that:

i. The Salk type vaccine should be persisted in, during the period of transition.

ii. The oral vaccine should be taken in addition to the Salk vaccine.

iii. Only type 1 attenuated vaccine has been issued in the first place because most of our epidemics have been due to this strain. This does not guarantee that all future epidemics will be due to type 1. It, therefore, emphasizes the need to maintain protection with the Salk vaccine at present.

iv. The oral vaccine can be taken without any hazards when other injections are being given.

v. The second and third oral doses which will be administered in 1961 will contain all 3 types and not type 2 and type 3 respectively.

vi. Children who are febrile should not receive the vaccine.

vii. Pregnant women may take the vaccine with safety.

viii. It has not as yet been feasible to make the vaccine available to private practitioners, but this will be done if the organizational difficulties can be overcome.

We would emphasize, however, that there are certain groups which are specially at risk, e.g. patients on steroid therapy and those who have recently undergone surgery or other stressful situations.

The South African vaccine contains small amounts of penicillin and streptomycin. Children known to be allergic to oral penicillin should probably not receive the oral vaccine.

It also appears that the original plan to feed the vaccine to neonates, thus rendering all infants immune, is feasible. Indeed, some authorities regard it as essential for all children between 3 and 6 months old to be immunized, otherwise it will never be possible to produce an immune community, with the consequential (possibly catastrophic) hazards

menacing the unprotected as a result of exposure to the virulent, wild strains.

In Israel there has been no difficulty about including the 3–6 month age group in the immunization campaign.

The success of the campaign depends on the administration of the vaccine to the whole of the population at risk. This is an important consideration in respect of the safety of the procedure as the oral vaccine is excreted in the stools and the strains thus have a capacity to spread.

No scientific evidence about the immunological efficacy of the South African vaccine has been made available to the medical profession. It would be desirable to know, e.g. what antibody response occurs when the vaccine is administered to triple-negative subjects, i.e. persons whose sera do not contain any antibodies to the three types of polio virus; nor do we know for how long antibodies which may be produced by live vaccine will persist. The available evidence covers only relatively short periods of time. Teelock[1] has recently reported on a poliomyelitis epidemic in Mauritius, where a Koprowski-Sabin type of vaccine (manufactured in South Africa) was given to the population but only when the outbreak had virtually come to an end. In the Mauritius epidemic 4 cases of poliomyelitis occurred after the use of this South African vaccine. In two of the cases the children (each aged 3 years) were already ill before vaccination. In the other two cases there was no history of illness before vaccination but the vaccine was given only 13 days before the onset of the illness.

There is evidence that the strains spread freely within a household or among the members of a closed institution, e.g. an orphanage, but spread between families does not occur with regularity. It, therefore, seems likely that every person seeking oral vaccine protection against poliomyelitis will have to ingest the live vaccine personally.

It is undesirable to feed the attenuated strains in the summer months, as has been done this year, because the prevalence of other enteric viruses is likely to interfere with the establishment of the polio virus in the alimentary tract.

Had adequate steps been taken to issue a scientific statement to all medical practitioners, an adequately informed profession would have been able to co-operate with the public authorities.

This is the second occasion on which an anti-polio immunization campaign has been embarked upon in this country without adequate briefing of the profession beforehand. In 1955, in relation to the launching of the Salk vaccine, we made available[2] to the profession for the first time in South Africa the basic information necessary to assist our colleagues in making up their minds on the use of the vaccine. On this occasion the profession has again had to take its cue from information released in the lay press—an unsatisfactory, undesirable and inadequate way in which to attempt to instruct a professional group on a technical matter.

The memoranda which have been made available to the medical press and the medical profession were released after the campaign was virtually over and had met only with a very qualified success.

There seems to have been adequate immunization of the school-going population, but results were disappointing with pre-school children. A very considerable section of this community could have been reached in the registered nursery schools, where they provide a suitable captive population. Any campaign should also take account of the inevitable absenteeism from school on any one day, a situation easily remedied by a simple plan to immunize these children in the succeeding week of the campaign.

With whatever urgency it was necessary to embark upon the polio vaccination programme (and as we have indicated, its wisdom at this time of the year was doubtful), it remains a most unfortunate omission that no previous steps were taken to reach the medical profession in good time before the campaign was started.

It is urged upon the authorities concerned with the organization of anti-polio immunization campaigns to inform the medical profession adequately about all scientific aspects of the campaign in good time before it is undertaken. In this way every medical practitioner can be persuaded to become an active participant in propagandizing the public, without whose whole-hearted co-operation and support such a project cannot succeed.

1. Teelock, B. (1960): Brit. Med. J., **2**, 1272.

2. Editorial (1955): Medical Proceedings, **1**, 129.

(*Vervolg op bladsy 590a*)

The Tables reflect a clinical impression based on daily clinical observations. The authors state, however, that it is difficult to set out such findings in Tables, the more so as many patients were labelled 'hopeless.' A few cases are reported in more detail, including laboratory data, demonstrating impressive results.

The side effects which were observed were related to the mucosa of the intestinal tract with the development of stomatitis and diarrhoea with mucus and blood, and leukopenia.

No conclusive opinion can be formed from the results. It would appear, however, that Endoxan is one of the most effective of the currently available drugs. Leukaemias and the closely related reticulum cell and lymphoma groups are most sensitive. Amongst the carcinomata, stomach and breast cancer are perhaps most suitable.

Secondaries in the liver were possibly more resistant. Primary liver carcinoma responded best to 5-fluor-uracil.

The role of roentgen therapy is difficult to assess. It is possible that irradiation makes cells more responsive to chemotherapy.

The authors feel that if relief of pain and a *full* life for the remaining years can be obtained, instead of the addition of a few more years to the patient's life, something worthwhile has been achieved, and chemotherapeutic treatment justified.

ANTIMICROBIAL DRUGS IN LUNG INFECTIONS

A COMPARATIVE STUDY OF PENICILLIN, SULPHONAMIDES, ACHROMYCIN, ERYTHROMYCIN, CHLOROMYCETIN AND ALBAMYCIN T

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At the commencement of the experiment the author undertook to determine whether sulphonamides and penicillin of different types were satisfactory for various types of respiratory infections.

It was decided that every patient admitted to the non-European section of the Boksburg Hospital with lung infection was to be assigned to either 'A' or 'B' treatment.

'A' treatment consisted of sulphadiazine in a mixture with equal parts of potassium citrate. The dosage was 1 c.c. per lb. body weight, divided into 4 and given every 6 hours (4 c.c. contained 0.5 g. of sulphadiazine).

In 'B' treatment the child was given 250,000 units of penicillin 6-hourly irrespective of weight or age. If a child was acutely ill, he was put on to A + B treatment.

Each child had an X-ray and a throat culture done. The number of days the temperature remained elevated was recorded.

The bacteriological examination was discontinued after 25 cases because the results in nearly all cases showed a mixed flora of *Pneumococcus catarrhalis Streptococcus viridans*, non-haemolytic streptococcus, pneumococcus and coagulase-positive staphylococcus. In no case was a pure culture of a single organism found.

Table 1 shows 7 cases treated on the A and 27 with the B regime (4 others died). 7 cases (6 others that died) were treated with A and B simultaneously. The cases that died were excluded from the study. As seen from the final average, the length of time the temperature was elevated in A was 2.4 days, in B 2.3 days and in A + B 2.5 days. It could have been expected that A + B should have been longer as it contained the more severely ill patients, but this was offset by the fact that 6 of a total of 13 died.

As the results were very satisfactory, the treatment was then changed to C and D (Table 2).

'C' consisted of 1 tablet of Lederkyn on the first day followed by a half tablet daily on subsequent days.

In 'D' treatment 600,000 units of procaine penicillin were given by intramuscular injection once daily.

TABLE 1

	A=SULPHADIAZINE		B=PENICILLIN	
	A	*B*	*A+B*	*Total*
Number of Cases	7	27+ (3 died)	7+ (6 died)	41+ (9 died)
Pneumonia	2	7	2	
Broncho-pneumonia	4	12	3	
Bronchitis	1	8	2	
Total (Days)				
Pneumonia	4	15	11	
Broncho-pneumonia	12	32	7	
Bronchitis	1	13	2	
Average				
Pneumonia	2	2·1	5·5	
Broncho-pneumonia	3	2·7	2·3	
Bronchitis	1	1·6	1·0	
Total Average days	2·4	2·3	2·5	

This showed that the results with the long-acting sulphonamide and long-acting penicillin were equally satisfactory.

As a final test 19 cases were treated with Distaquaine V 120 mg. 6-hourly (treatment E). The results in this group were a little better than any of the others and gave an average elevation of 1.7 days per case.

TABLE 2

C=LEDERKYN D=PROCAINE PENICILLIN
E=DISTAQUAINE V

	C	*D*	*E*	*Total*
Number of Cases	34	38 + (4 died)	19	91+ (4 died)
Pneumonia	13	13	3	
Broncho-pneumonia	14	10	8	
Bronchitis	7	15	8	
Total (Days)				
Pneumonia	33	26	8	
Broncho-pneumonia	20	23	10	
Bronchitis	11	27	15	
Average (Days)				
Pneumonia	2·5	2·0	2·7	
Broncho-pneumonia	1·4	2·3	1·3	
Bronchitis	1·6	1·8	2·0	
Average (Days)	2·2	2·0	1·7	

After these very successful results with penicillin and sulphonamides in lung infections, it was decided that these findings should be compared with the different 'mycins'. As the severity of infection may vary from year to year, it was considered essential that the drugs to be compared should be investigated simultaneously. This experiment was undertaken at the non-European Children's Section of the Boksburg Hospital. During the period May 1959 to April 1960, 1,093 children and infants were admitted under the author's care. A total of 146 died within 48 hours of admission and 140 died after 48 hours. The total deaths were 286, a death rate of 26.2%. In nearly every instance the death could be attributed to malnutrition, with and without gastro-intestinal complications.

At the start of the test 4 drugs were compared:

1. Achromycin Syrup, 125 mg. 6-hourly.
2. Chloromycetin Palmitate, 125 mg. 6-hourly.
3. Procaine penicillin, 600,000 units once daily;
4. Madribon tablets, 1 initially and then ½ daily.

Later, as the drugs were made available:

5. Erythromycin Syrup, 200 mg. 6-hourly;
6. Albamycin T, 125 mg. of Albamycin and 125 mg. of tetracycline 6-hourly.

The cases were taken in turn on admission and were unselected. The decision rested with the nursing staff at the time of admission. All cases which showed evidence of lung infection were included in the series.

Instructions were left that no case was to be treated before the following had been done:

1. A straight X-ray of the chest;
2. A full blood count and sedimentation rate;
3. A Mantoux test (1 : 1,000).

The project was unusual in that no case in the series had a positive Mantoux test. This is interesting because in another series of 500 African children who were Mantoux-tested, 35% had a positive result. This was in a higher age group (6–10 years).

No cases died before treatment was commenced. Instructions were also given that if a child was very ill, treatment was to be commenced immediately. A few cases were so treated.

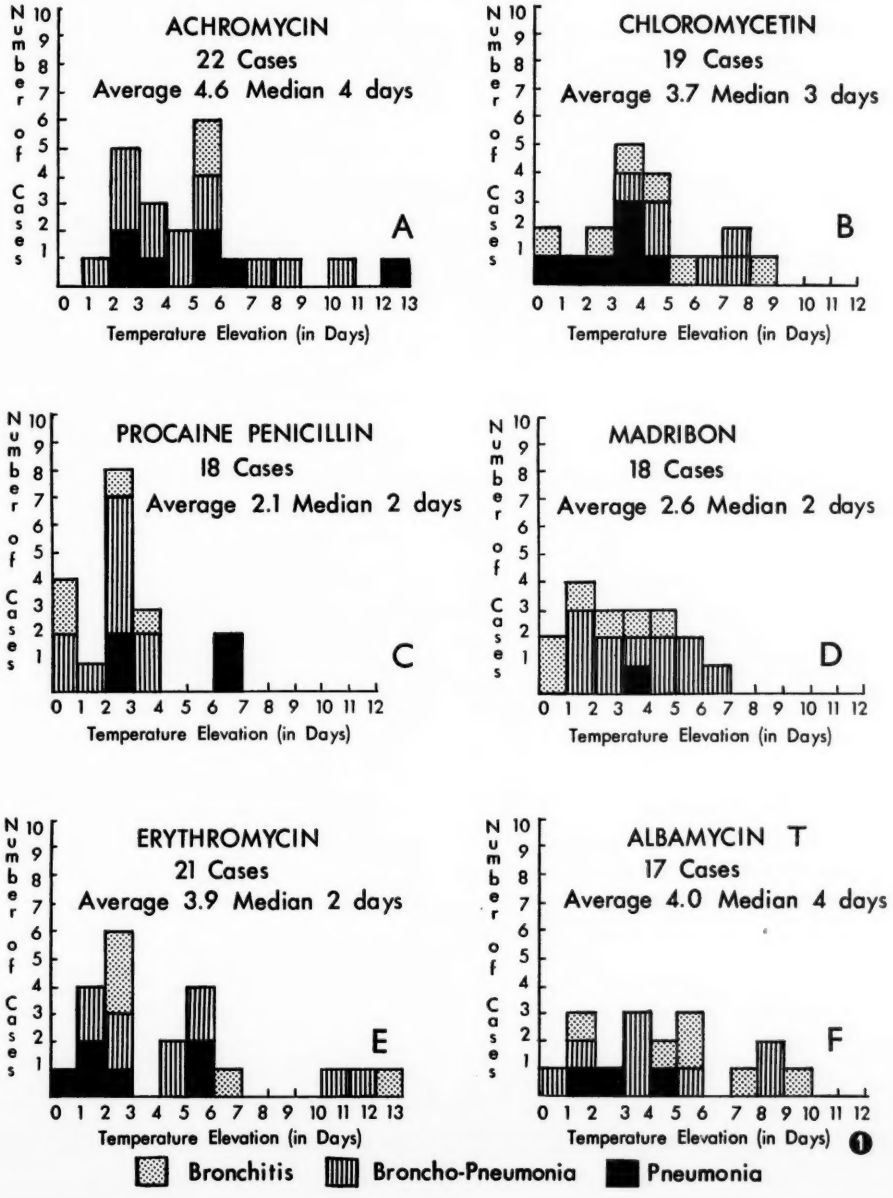
Although some cases were acutely ill, no case was given a second antimicrobial agent and all cases made a clinical recovery. In comparison with the first project, there were no deaths in this series There were no relapses or complications such as staphylococcal abscesses or pleural effusions. Cases which appeared to have measles or whooping cough, in a few instances, were excluded as they were transferred to the Isolation Hospital.

The final diagnosis is not entirely satisfactory in view of the fact that only an AP X-ray view of the lungs was taken. It was therefore possible that a number of cases may, with further views, have had the diagnosis changed from bronchitis to broncho-pneumonia, or even from broncho-pneumonia to pneumonia. When the detailed charts are compared, it is seen that the cases are not strictly comparable as the number of cases of bronchitis, broncho-pneumonia and pneumonia differ in the various groups. This is not of great consequence because the same error would be present in all instances. In a number of cases where the X-rays were repeated 5–7 days after the first X-ray, it was found that, in spite of the fact that the clinical findings and temperature had gone back to normal and the X-rays showed improvement, there was still a great deal of underlying pathology.

The physical examination of the chest was most unsatisfactory because, in many cases, the findings differed greatly from the X-ray findings. Bronchial breathing in cases of pneumonia and broncho-pneumonia was often not present. If present it did not last for more than 24 hours. In all cases in the series some evidence of lung infection was present, i.e. cases of tonsillitis, otitis media and influenza as the primary infection were not included in the series.

A very interesting finding, which was most striking in the series, was that in many cases the child had a very high admission temperature and in spite of *no* treatment at all the temperature had come down to normal before the actual treatment was commenced. This emphasized a most important point, viz. that in many instances bed-rest alone can lower the temperature a great deal.

The dosage of the drugs recommended was considered adequate, irrespective of the age of the patient, and also simplified the whole programme. In no instances were any toxic or side effects reported. The other ancillary treatment given in a number of cases was oxygen, also steroids if superadded bronchospasm was present. Vi-daylin as a vitamin supplement was given in many instances. As



cough was not troublesome, no cough mixtures were given.

The results (Fig. 1) can be summarized as follows (Table 3):

acting drugs and also with oral penicillin in the form of Distaquaine V.

In the case of Chloromycetin, Achromycin and Albamycin T, the schedule of treatment is

TABLE 3: ANALYSIS OF VARIANCE OF DAYS OF TEMPERATURE ELEVATION

Drug	*Achromycin*	*Chloromycetin*	*Procaine Penicillin*	*Madribon*	*Erythromycin*	*Albamycin T*
	1	2	3	4	5	6
No. of Cases	22	19	18	18	21	17
Average Age (Years)	2·7	2·6	2·7	3·2	1·4	4·2
Σx	101	69	38	47	83	69
Σx^2	623	341	132	177	569	399
Mean	4·59	3·63	2·11	2·61	3·95	4·06

x = Number of days of temperature elevation

Variance Ratio $\frac{16 \cdot 96}{6 \cdot 56} = 2 \cdot 58$. $P < \cdot 05$

t test between penicillin group and each 1, 2, 5 and 6 is significant. ($P < \cdot 01$, $\cdot 1$, $\cdot 05$, $\cdot 05$).
t test between Madribon group and each of 1 and 6 is significant ($P < \cdot 05$, $\cdot 05$).

It appears that the results were better with penicillin and Madribon. Although the patients treated with Erythromycin had a lower average age of 1.4, this was not the cause of raising the average length of elevated temperature. The cause was mainly due to the cases whose temperature was elevated 10, 11 and 12 days respectively.

THE HAEMATOLOGICAL PICTURE

The average haemoglobin level in the 6 therapeutic agents is essentially similar, except that in the case of Erythromycin, the level is a little lower at 10.39. This may be due to the fact that with this drug the average age of the patient was markedly lower than any other group.

The average white blood count in all instances was above 12,000 c.mm., indicating that there was some bacterial infection. This was borne out by the differential count in most instances. These figures were, however, not reported. The evidence of bacterial infection appears to have been substantiated by the average sedimentation rate which was above 30 mm. The clinical response, X-ray report and blood findings suggested that in nearly all instances the underlying pathology was not attributed to virus infection in any but a few instances.

SUMMARY AND CONCLUSIONS

The results of the treatment in both projects substantiate the original hypothesis that sulphonamides and penicillin are adequate therapy in severe forms of lung infections when given singly. The results are equally good with long-satisfactory in that there were no deaths, no complications and all cases made complete recovery. Erythromycin is in an intermediate position bescause the average result was 3.9 days.

All cases should in the first instance be treated either by penicillin or sulphonamides. The value of combined therapy has not been assessed in this sense, but from personal experience, the addition of a second antimicrobial agent has conferred very little dramatic benefit in many instances.

As the results on the whole in the second project were so satisfactory, it can be accepted that nearly all cases can be treated as outpatients without any detriment to the patient. The only exception would be acutely ill patients who required oxygen.

The majority of non-European patients die of malnutrition. This is an economic rather than a medical problem.

An interesting observation was that in many instances the admission temperature was frequently very high and yet with only bed-rest the temperature became normal before any therapy was given. This means that one must be most cautious in attributing sudden improvement to the therapeutic agent.

I wish to express my thanks to the Superintendent of Boksburg Hospital, Dr. B. M. Burger, for permission to submit this paper for publication; to my colleagues Dr. F. Meltzer and Dr. S. Manaschewitz for their able assistance; to Sister Martha Mokgatla for her co-operation and great assistance with the records; also to the following drug companies for supplying a great deal of the therapeutic drugs: Roche Products Ltd., The Upjohn Co. (Tuco), Lederle Laboratories, Abbott Laboratories and Parke, Davis Laboratories.

I am indebted to Dr. A. M. Adelstein for the statistical analysis.

COMPLETE ABORTION COMPLICATED BY HYPOFIBRINOGENAEMIA

REPORT OF A CASE

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In 1901 De Lee described a case in which the patient died from post-partum haemorrhage despite a well contracted uterus. He ascribed it to a 'haemophilia-like' phenomenon. In 1937 Dieckmann suggested that such unexplained, uncontrollable haemorrhage could have its origin in a decrease or absence of fibrinogen. It was as recently as 1949, however, that Moloney *et al.* first treated a case successfully with fibrinogen by infusion.

Since that time many cases have been described, but it is felt that there is an actual increase in the incidence in spite of better diagnosis and recognition of the condition. In a series of 8 cases collected by Scott from 1937 to 1955, only 1 occurred before 1951, and he explained this by the increased use of large molecular substances such as Dextran. The fibrinogen is supposedly precipitated as an insoluble fibrinogen-Dextran compound.

CASE REPORT

A Bantu women, M. M., was referred to the Gynaecological Ward at 5 p.m. on 30 March 1960. The diagnosis was severe post-abortum haemorrhage.

History. The patient had not menstruated for 5 months. A 8 a.m. on the day of admission she experienced lower abdominal colic which steadily became worse until, 4 hours later, a fleshy mass was passed *per vaginam.* This was accompanied by severe bleeding which continued unabated. When, during the early afternoon, she started to feel weak and dizzy, an ambulance was summoned which brought her to hospital at 4.30 p.m.

Last Menstrual Period: October 1959.

She had had one child 7 years before. There had been no previous miscarriages.

Examination. The patient was a normal Bantu woman of small stature. The skin was cold and clammy and the mucous membranes were pale. She looked shocked and distressed. The pulse-rate was 100 per minute; blood pressure, 70/40 mm. Hg; Hb, 40% (Haldane) and the sedimentation rate 20 mm. in the first hour.

The uterus was palpable on abdominal examination, and although it felt hard and well contracted, clots could be expressed.

On vaginal examination it was found that she was bleeding profusely from the uterine cavity. There were no cervical tears. On bimanual examination the uterus was estimated to be the size of a 14 weeks' pregnancy. The vaginal fornices were normal.

Fortunately the patient had brought along the expelled products. These consisted of a foetus (crown–rump length: 21 cm.) to which the complete placenta and membranes were still attached.

Special Examinations. Approximately 10 ml. of blood were withdrawn from the antecubital vein, 2 ml. of which were used for grouping and compatibility tests; 3 ml. were transferred to a test tube and slowly rotated whilst the time was noted. Another 2 ml. were collected in an oxalate tube for fibrinogen determination. A further 2 ml. were collected in an oxalate tube for the Fibrindex test.

1. *Clotting Time*: After 16 minutes no clot was visible and the blood was uniformly fluid. There was still no coagulation after 1 hour.

2. *Fibrindex Test*: The test performed on the patient's serum showed no clotting with the Fibrindex solution. It was therefore evident that the fibrinogen was below the critical level and it was decided to administer fibrinogen without delay.

3. *Plasma Fibrinogen Level*: This was 9 mg. per 100 ml.

Treatment. An intravenous infusion of reconstituted plasma was immediately set up, and this was followed by compatible whole blood. Ergometrine 0.2 mg. was given intravenously and 0.2 mg. intramuscularly.

Two bottles of Parenogen (Cutter) containing 1 g. fibrinogen each, were administered rapidly through a Y-connexion into the same vein.

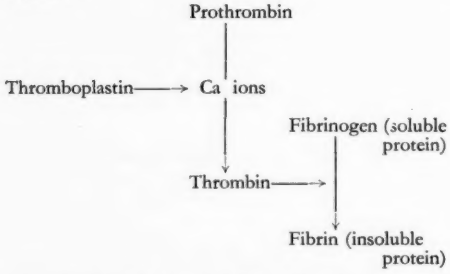
The patient's condition improved rapidly. The vaginal haemorrhage diminished and stopped after 35 minutes. The blood pressure rose to 110/80 mm. Hg, and the patient's general appearance improved considerably.

During the following 24 hours the urinary output was 1,800 ml.

Fibrinogen determinations were as follows:
1st Day: 0 mg. per 100 ml. It was later thought possible that this figure could have been due to a technical error. Instead of the usual 2 ml., about 4 ml. of blood were added to the oxalate tube. This may have resulted in clotting with depletion of fibrinogen in the tube.
2nd Day: 132 mg. per 100 ml.
3rd Day: 183 mg. per 100 ml.
The patient made an uneventful recovery and was discharged on the fourth day.

THE NORMAL BLOOD COAGULATION MECHANISM

Although there have been many alterations and additions to the scheme as originally propounded by Morawitz in 1905, the basic steps remain the same and can be summarized as follows:



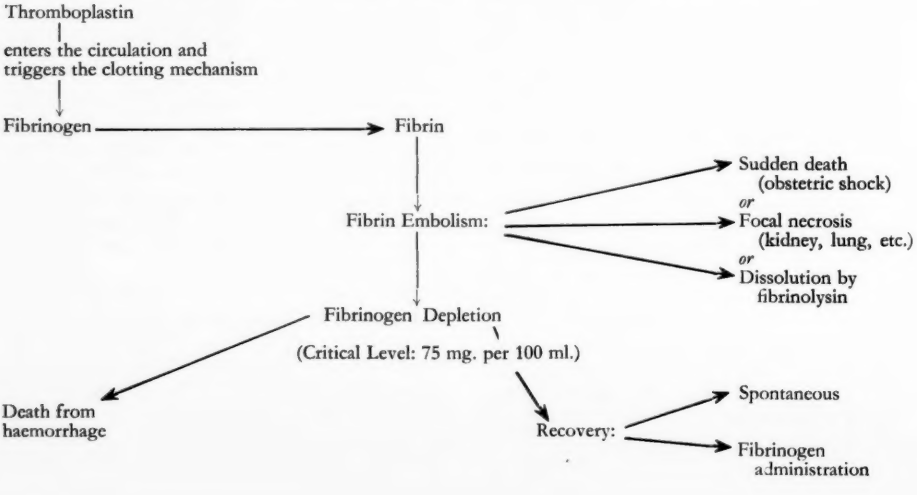
Thromboplastins are derived from:
Amniotic fluid;
Blood platelets and fragments of blood clot;
Injured tissue, including uterine muscle in severe hypertonus;
Placental tissue; and
Decidua.

Fibrinogen (normally found in the plasma in a concentration of 300–400 mg. per 100 ml.) is formed in the liver. Serial determination in cases of hypofibrinogenaemia have shown that the rate of formation in conditions of stress could be as much as 30 mg. per 100 ml. per hour.[1] Thus, if the cause can be eliminated, the patient would recover spontaneously in 4–5 hours. The much longer period needed to replace the other plasma proteins suggests that fibrinogen formation is part of a dynamic system. There seems to be a continuous microscopic precipitation of fibrin with immediate lysis on the one hand, and a continuous output of fibrinogen by the liver on the other.

The level of plasma fibrinogen below which there is a complete absence of coagulation is 75 mg. per 100 ml. At levels of 75–150 mg. per 100 ml. some degree of inadequate clotting will occur. Only above 150 mg. per 100 ml. will the normal mechanism come into play and haemostasis be effected.

THE MECHANISM OF PRODUCTION OF HYPOFIBRINOGENAEMIA [2]

Fibrinolysin. It has been suggested that the substances liberating thromboplastin also contain an activator for the fibrinolytic enzyme system.[3] In cases of amniotic fluid embolism the enzymes formed in this way can dissolve fibrinogen as well as fibrin. Not only are the large amounts of precipitated fibrin thereby dissolved, but also any remaining or newly formed fibrinogen. This coincident action of thromboplastin and fibrinolysin could explain the difficulty of obtaining post-mortem histological evidence of fibrin embolism.[4]



Causes. In 3 important clinical conditions thromboplastic material can enter the circulation and initiate the reaction, viz.:

1. Amniotic fluid embolism;
2. Accidental haemorrhage;
3. Missed abortion.

1. AMNIOTIC FLUID EMBOLISM

This is a condition of acute defibrination.[1] In cases where the uterus is contracting rapidly or with great force, amniotic fluid is forced through minute fissures in the membranes. By dissecting in the space between the membranes and the uterus the fluid reaches the placenta where it enters the maternal circulation either through the marginal sinus or the intervillous space.[6] After the membranes have ruptured fluid can also enter the circulation through the endocervical veins exposed by dilatation of the cervix. Because of the large amounts of fluid implicated, the term 'amniotic fluid infusion' seems the better one.[7] In this way the maternal blood is flooded with thromboplastic material which causes fibrin embolism. This embolism is especially evident in the arteries and capillaries of the lungs where it causes an acute cor pulmonale.

Two other factors are also implicated in making the lungs the target organs, viz. an anaphylactoid reaction to amnion debris and true embolism from particles in the fluid.[8] Therefore the clinical picture is one of an acute pulmonary lesion,[5] viz. shock, dyspnoea, cyanosis, and anoxic convulsions. Most patients usually succumb at this stage before anything can be done. The survivors often develop fibrinogen depletion and haemorrhage.

Because this catastrophe usually takes place during labour, the best obstetrical treatment is to rupture the membranes. Sedatives, antispasmodics, intravenous cortisone, oxygen and blood should be administered as soon as possible. If there are signs of recovery from the acute episode, fibrinogen should be given without delay.

2. ACCIDENTAL HAEMORRHAGE

This is a condition of subacute defibrination. Five per cent of patients with premature separation of the placenta develop a haemorrhagic tendency.[9] In a large number of cases the fibrinogen level will be lowered in relation to the degree of separation. For bleeding to take place, however, at least 50% of the placenta must be separated.

The decidua basalis is split in two by the haematoma and perforations are caused by the increased pressure at various places in the outer layers.[10] In this way blood and decidual debris enter the maternal circulation via the choriodecidual space. Again the mechanism is triggered, but not at such a rate and to such a degree as in amniotic fluid embolism. A more gradual conversion of fibrinogen to fibrin takes place with resultant derangement of coagulation and haemorrhage. It is of interest that hypofibrinogenaemia does not occur in conditions where the blood can escape through the cervix, as in placenta praevia or marginal sinus rupture.

The treatment of accidental haemorrhage is influenced by the high incidence of coagulation defects. It is now generally accepted that the uterus should be emptied as soon as possible. Any fibrinogenopenia should be corrected and the membranes ruptured. This is done, firstly, to relieve intra-uterine pressure and, secondly, to induce labour. Caesarean section is resorted to if the baby is alive and there is reason to believe that vaginal delivery is not imminent. Caesarean hysterectomy should never be necessary, even in severe 'utero-placental apoplexy,' because recovery can be expected as soon as the uterus has been emptied and the fibrinogen restored to normal.[11]

3. MISSED ABORTION

This is a condition of chronic defibrination. In contrast to amniotic fluid embolism and accidental haemorrhage, the development of hypofibrinogenaemia in missed abortion is not influenced by maternal trauma or uterine contractions. The thromboplastins are derived from the products of aseptic necrosis of the placenta and decidua. This takes about 4 weeks to become established. From that time onwards small amounts of thromboplastic material continually enter the circulation, causing a very gradual depletion of fibrinogen. Frequently the first signs of impending disaster are purpura or haematuria.

Whatever line of treatment is adopted, it is important to determine the plasma fibrinogen level and, if necessary, to correct any deficiency. If it is decided to await events, regular fortnightly determinations should be done and fibrinogen given if the level falls below 150 mg. per 100 ml. If signs of haemorrhage occur, the uterus should be emptied without delay.

It is important to realize that post-partum haemorrhage can be a serious complication in all three of the afore-mentioned conditions. However, if fibrinogen is administered, the cessation of bleeding is often dramatic and complete.

Although the conditions mentioned constitute the more frequent causes of hypofibrinogenaemia, the latter may occur in a variety of other conditions, viz.: severe liver damage (Wintrobe, 1951); prostatic carcinoma (Trautwein, 1930); pulmonary surgery (Penn and Walker, 1954); as well as leukaemia, hydatidiform mole and, last but not least, abortion. A condition of congenital hypofibrinogenaemia also occurs, and 22 such cases have been described (Wilson and Gutteridge, 1956).

DIAGNOSIS

About 8 ml. of blood are withdrawn from a suitable vein and divided as follows:

(*a*) 2 ml. for grouping and compatibility.
(*b*) 2 ml. for the clot observation test.
(*c*) 2 ml. (in an oxalate tube) for the Fibrindex test.
(*d*) 2 ml. (in an oxalate tube) for fibrinogen determination.

1. *The Clot Observation Test* (*Weiner*). The tube is slowly rotated and the time noted. Normal blood clots within 10 minutes, the clot remains firm and shows a retraction of 40% after 1 hour. If fibrinogen is decreased, either no clot is formed or a soft mass forms (after a variable period) which is again dissolved. Ideally the blood should be incubated for 1 hour at 37° C., but this practical difficulty is overcome by placing the tube in a shirt or vest pocket and examining it at intervals.

2. *Fibrindex Test* (*Ortho*). By adding oxalate to the blood, the formation of thrombin is prevented. If a standard amount of thrombin is now added, the degree and speed of clotting will be a direct indication of the amount of fibrinogen present. Fibrindex is pure human thrombin, standardized so that the test will be normal if the fibrinogen concentration is more than 150 mg. per 100 ml. If it is decreased, the test will be prolonged, and if it is less than 75 mg. per 100 ml. no clotting will occur.

The test is done as follows:

The oxalate blood is centrifuged and 2 drops of the supernatant fluid are placed in a small test tube. Two drops of dissolved Fibrindex are added and the time taken.

Normally a firm clot forms within 10 seconds, and it cannot be dislodged from the glass by light tapping after 50 seconds. If no clotting occurs, it can be assumed that the plasma fibrinogen is below the critical level.

3. *Fibrinogen Determination.* The result of this laboratory test can usually be obtained within 2 hours.

The bleeding time and Hess's capillary test should be done to complete the investigation.

TREATMENT

1. *Fibrinogen Administration.* This is available in bottles of 1 g. (Parenogen, Cutter) with the diluent. Instructions for reconstitutioning are provided. It is usually given as a 2% intravenous infusion (through a Y-connexion) with the blood. It has been found that, in most of our cases, 2 g. were sufficient to control haemorrhage.

2. *Plasma.* If fibrinogen is not available, plasma can be given, preferably in double or quadruple strength. It should be used in any case until the blood arrives, instead of the usual dextrose in water.

3. *Blood.* This is given mainly to replace the blood loss. It is useless as a source of fibrinogen unless it can be administered within one hour of withdrawal from the donor.

SUMMARY

A case of complete abortion complicated by hypofibrinogenaemia is presented.

The 3 conditions commonly responsible for hypofibrinogenaemia are amniotic fluid embolism, accidental haemorrhage and missed abortion, but it can occur in other conditions.

Some points of interest in the treatment are stressed.

The mechanism of production of hypofibrinogenaemia is briefly reviewed.

I wish to thank Prof. F. G. Geldenhuys for his advice in compiling this report, as well as Dr. M. M. de la Harpe, under whose care the patient was admitted, for permission to submit this case report for publication.

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THE NATURE AND MEASUREMENT OF PRIMARY PIGMENTATION

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About 6 years ago Kooij and Scott[1] showed that primary pigmentation could readily be evoked in the skin of Bantu and Coloured subjects regardless of sex or age. This phenomenon is nothing other than a prompt and readily visible darkening of the skin on exposure to certain long ultraviolet rays. It does not occur so regularly in Whites. It depends apparently on a photo-oxidative darkening of the formed melanin granule.[2] The threshold energy required at 340 mμ for this darkening in Whites is given[3] as 200 × 10^6 erg/cm.^{2} Values for Bantu skin are not known, but Kooij and Scott showed that the darkening reaction underwent a prompt spontaneous reversal within a day in most cases. In Whites this pigment darkening lasts longer.

Primary pigmentation occurring *in vivo* depends on factors of which we know very little. Access of oxygen from the air or the blood seems to be essential, since compression of the skin by a quartz window suppresses the reaction of darkening to the ultraviolet rays.[2] No quantitative data on the oxygen requirements are available, but polarographic studies may perhaps yield suitable information. Presumably the appropriate intracellular redox potential is responsible for the spontaneous lightening which follows photo-oxidation, but no data are available on this subject either. Nonetheless, the paling and darkening steps are not limitlessly reversible, since the granule tends to become more stable in the dark form at each re-exposure to light.[4] Most writers agree that the oxidative colour changes result from a non-enzymatic auto-oxidation related to, if not identical with, a similar darkening of melanin seen on exposure to heat in the presence of oxygen. However, the action of light in loosening or tightening the cytoplasmic gel *in vivo* cannot as yet be excluded in bringing about colour changes through a redistribution of the melanin granules within this gel.

Artificial production of pale melanin with reducing agents such as dithionite may produce substances similar to the naturally occurring paler melanins. Edwards *et al.*[5] suggest that a pigment which they identified spectrophotometrically in 1939 in the living skin, which they called melanoid, may be none other than reduced tan-coloured melanin. Melanin reduced artificially with dithionite gives, at any rate, a similar absorption spectrum. A reductive potentiality of this kind *in vivo* would enable melanin to act as an absorber of electrons,[6] reduction being synonymous with electronation, a process of possible importance in preventing radiation damage.

A more thoroughly investigated aspect of the problem is the de-electronation (oxidation) of melanin with its corresponding reduction of an electron acceptor. This process may or may not be associated with a change in colour of the melanin, and stepwise oxidations of pale melanin can first produce darkening followed by decolorization.[7] Illustrating this process, the argentaffin reaction of melanin granules has nothing to do with silver affinity as such, but merely refers to the power of melanin to reduce both simple and complex silver cations at various pH values to metallic silver. Usually it is assumed that the silver precipitates *in situ*, but a partial binding (argyrophilia) is not excluded. Because melanin can act as a cation exchanger and can form chelates of heavy metals, the possibility of such binding certainly arises. The terms *argentaffin* and *argyrophil* may thus provisionally be classed as aspects of reducing power and chelate formation respectively in the melanin granule.

The foregoing considerations of the histochemistry of melanin apply as well to the discovery made by Lillie[8] that melanin binds ferrous iron. This bound iron was then capable of giving a Turnbull blue reaction with ferricyanide. The ferrous iron of haemoglobin does not react in this way, all 6 possible dative bonds of the iron being fully co-ordinated. A partial co-ordination in melanin of ferrous iron is thus highly probable. A full 'inner complex' co-ordination is a structural impossibility since no octahedral binding arrangement similar to that of a haemoglobin is to be found in melanin. Generally it is supposed that the chelated iron is 'eluted' by the acid added to the ferricyanide solution and then precipitated

in situ by the ferricyanide itself. The structure of the blue ferricyanide salts is such that persistence of a partial bonding of the iron to the melanin polymer does not seem possible.

As in other situations involving high polymers, the genetic control of polymerization influences the range of these reactions markedly from one species to the next and among differently melanized tissues. Although ultraviolet light is known to influence the polymerization of plastic monomers,[9] it is not known whether a similar change takes place in the melanin granule through the action of light. More usually the colour reactions would be ascribed to the oxidative changes as illustrated in dopa-melanin, where the o-quinone form (with its reduced, semiquinonoid forms) is derived from the 5, 6-dihydroxyindoles by oxidative steps.[10] Internal stabilization of the melanin polymer by resonance forms, may also greatly affect the oxidizability of melanin with or without the presence of a metal chelate. This resonance stabilization influences metal chelate stability in dyestuffs, and is associated with colour changes.[11] Little can at present be added to these possible mechanisms for the reaction under discussion.

METHODS

In the present study, primary pigmentation in the Bantu was studied during May 1960 in Pretoria (latitude 25°45′ South, altitude 4,340 feet). Experiments were done in the late mornings, at the solar altitudes given in the results. On two successive mornings an area 3 inches × 6 inches was exposed on one or other side of the back, with the subject's spine parallel to the shadow of a vertical object. Exposures lasted 30 minutes, and were followed immediately by reflectance spectrophotometric readings.

To measure the pigment in the skin, reflectance spectrophotometry using a red glass filter (Corning 2403) has been advised.[12] Having a Brinkman cyclops oximeter[13] available (made by P. J. Kipp, Delft, Holland), we considered that it might be suitable for the purpose of pigment measurement. The apparatus is normally used for estimating the percentage oxygen saturation of blood passing through the skin capillaries, a procedure which requires an extremely sensitive reflectance in the red, where HbO_2 and Hb have widely separated extinction coefficients. The mobile eye or 'cyclops' measures red reflection by means of compensated barrier layer photocells incorporated in a small case with a tiny built-in light source, an Ilford 281 red filter and a surface aperture adapted for skin readings with contact occlusion and minimum compression. The oximeter is intended for use on fair-skinned subjects, and the current of the light sources and the galvanometer deflections are arranged accordingly. However, if it should be required, it seems feasible to use the compression plate (giving reflectance measurements under diascopic pressure) and the green (500 mμ) filter belonging to the oximeter for determining erythema as well as pigmentation in dark and blond skins. The green filter is designed to give minimum reflectance from both Hb and HbO_2 *equally* (i.e. at an isobestic wave-length) but only a tenth sensitivity is possible on the apparatus with this filter. Normally, the standards used in the oximeter are (1) the red and green reflectance of compressed (bloodless) skin and (2) the same values for hyperaemic skin, if necessary when pure oxygen is inhaled. Differences are then due purely to changes in vascularization and oxygen saturation. The colour due to melanin remains constant throughout.

To measure melanin only, we therefore ignore the factor of vascularization of the skin and tissue oxygen consumption, and calculate the difference between the red reflection only from normal and irradiated skin, as read in millimetres on the scale. Theoretically, a logarithmic absolute scale could be constructed, but for the present study, each patient's unirradiated skin served as the arbitrary standard. For each case, at least 10 unirradiated areas were taken around the irradiated area to secure an average control reading, and 6 within the irradiated field. The difference between these two average readings was taken as the measure of pigment increase for that subject.

During preliminary studies it became apparent that a high energy process such as primary pigmentation, when induced for rather short exposure times (30 minutes), would clearly produce changes that lie in the steep part of the curve of pigment production. In longer exposures, or with stronger sunlight, the process would take place at an ultimately slower rate, i.e. in the flatter part of the curve. Such a curve has been published by Schulze.[14] As a consequence, small reductions in radiant energy acting on the surface caused by the curvature of the back in flexion or on the rib curvatures, or with a slightly projecting scapula, could cause gross differences in pigmentary response. This is the expected consequence of Lambert's law, by which it may be shown that the radiant

energy delivered per unit surface will fall in proportion to the cosine of the angle of incidence as measured from the normal. The patients were therefore positioned so as to have a normal incidence of rays somewhere about the centre of the test area.

Each of the 5 patients ultimately tested was studied on 2 consecutive days, as indicated. The only variable deliberately introduced was the blood level of vitamin A. The vitamin A assays were made by the antimony trichloride method described by Varley,[15] using Roche standards for calibration, due allowance being made throughout for the carotene levels also present in the blood. A large oral loading dose of vitamin A was given 3–4 hours before the assay, and the assayed value represents the blood level at the time of sun exposure.

RESULTS

These are set out in Table 1.

TABLE 1

Test No.	*Sex, Age (Bantu Subjects)*	*Solar Elevation*	*Plasma Vitamin A (μg/100 ml.)*	*Mean Galvo. Deflection Difference (mm.) Irradiated to Unirradiated Skin*
1	Male 30	33°	21	21
2			800+	20
3	Male 47	37°	32	21
4			800+	18
5	Male 28	31°	50	13
6			700	13
7	Male 14	30°	42	11*
8		33°	1000±	26
9	Male 13	33°	30	14
10		37°	1000±	13

* See comment in text.

COMMENT

From the results it is clear that reproducible degrees of primary pigmentation may be expected on successive exposures, and that the oximeter provides an extremely sensitive measure of pigmentation. It appears to be a more practical clinical instrument than the cumbersome though more versatile instruments described by Tronnier[16] for measuring skin colour.

A problem as yet unsolved is the phenomenon of immediate (heat) erythema in its relation to primary pigmentation. The results of experiments 7 and 8 in Table 1 illustrate an anomaly. The values for experiment 7 were taken from skin that was poorly pigmented but markedly erythematous. The following day (experiment 8) the skin pigmented extremely well, but showed no clinical erythema. A changing vasomotor tone thus seems capable of altering the degree of primary pigmentation. In none of the other test subjects was erythema seen clinically.

The effects of altering the blood level of vitamin A on primary pigmentation were obviously so slight as to fall within the range of experimental error. These slight differences would in any case not have been clinically perceptible. In 1937 Marchionini and Patel (quoted[3]) reported that mild solar erythema is accompanied by an increase and marked erythema by a fall in the serum level of vitamin A. The reverse experiment, viz. the influence of the serum level of vitamin A on solar reactions apart from primary pigmentation still remains to be done.

SUMMARY

Direct or primary pigmentation is a complex phenomenon which takes place in formed melanin, but whose exact mechanism is still uncertain.

A technique is described whereby primary pigmentation can readily be estimated from day to day with a high degree of reproducibility.

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GONADAL DYSGENESIS AND RENAL ABNORMALITY

A CASE REPORT

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and

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In addition to Turner's syndrome, various other congenital malformations affecting skin, skeleton, heart, blood vessels, the gastro-intestinal tract and the urinary system have been described in association with gonadal dysgenesis. From certain series of cases[1,2] it appears that 10–20% of cases of gonadal dysgenesis are chromatin-positive; also that other congenital defects are less common in chromatin-positive cases than in those with a male nuclear pattern. Recent technical advances in human genetics have focused interest on defects of sexual differentiation. This interest naturally includes the associated congenital anomalies. The following case of chromatin-positive gonadal dysgenesis showed abnormalities which were unusually gross for this type:

A 29-year-old Zulu woman was admitted to hospital with severe pneumonia which involved the right upper and left lower lobes. On treatment with oxygen, penicillin (0.5 M. units 6-hourly) and Sulphatriad there was no improvement; X-rays showed extension of the consolidation. On the third day treatment was changed to intramuscular chloramphenicol (0.5 g. 6-hourly) and cortisone (50 mg. 6-hourly). Her condition continued to deteriorate and she developed signs of peripheral vascular failure on the tenth day. The dose of cortisone was increased and streptomycin was added. She died 11 days after admission to hospital. A feature of the pneumonia was its spread despite energetic treatment. Culture of the sputum did not reveal the pathogen. The peripheral blood showed a polymorphonuclear leucocytosis with lymphopenia.

When she was admitted she was noticed to be very short with small, delicate feet and hands. Her breasts were completely undeveloped though the nipples were prominent. Pubic hair was scanty and axillary hair almost entirely absent. The external genitals were normal. There was marked bilateral webbing of the neck but no cubitus valgus.

She stated that she was the youngest, and the only girl, in a family of four. Her 3 brothers were of normal height. She had menstruated fairly regularly since the age of 15 years but her periods were scanty. She had never been pregnant. Six years before she had been in another hospital with swelling of the knees and ankles which had subsided on treatment and had not recurred.

The results of investigations done in hospital were as follows:

Haemoglobin: 12.9 g. %.

White blood cells (on admission): 14,600 per c.mm.

Polymorphs: 99%; Lymphocytes: 1%.

On the sixth day the total white cell count was 9,200 per c.mm., with 88% polymorphs, 9% lymphocytes and 3% monocytes. The polymorphonuclear cells showed a female chromatin pattern, 11% of 500 cells having 'drumsticks'.

E.S.R.: 35 mm. per hour (Wintrobe).
Urine: Albumin ++; no other abnormality.
Sputum culture showed normal flora. *M. tuberculosis* was not detected.
Wassermann Reaction: Negative.
Stool: Normal.
Blood culture: No pathogens detected.
Serum proteins: Albumin: 1.8 g. %; Globulin: 4.4 g. % (alpha$_1$: 0.6; alpha$_2$: 1.2; beta: 1.0; gamma: 1.6 g. %).
Successive X-rays of the chest showed a spreading pneumonia which initially involved the right upper and left lower lobes. The bones were not obviously osteoporotic.

The clinical diagnosis was severe pneumonia in a patient with chromatin-positive gonadal dysgenesis and Turner's syndrome.

At post-mortem examination the height of the body was 51 inches, the span 54 inches, and the distance from sole to pubis was 25 inches.

There was an extensive pneumonia involving the whole of the left lung and the right upper lobe.

The uterus was infantile. It was 50 mm. long and 30 mm. wide.

No true ovaries were present, but instead there was on either side a sausage shaped ridge of firm pearly-white tissue about 15 mm. long and 2 mm. wide. No follicles were present on the surface. These vestiges resembled the primitive gonadal ridges which are found in cases of gonadal dysgenesis.

No kidney was present on the left side. On the right there was a fused kidney with 2 renal pelves, the ureters from the 2 components joining above the lower pole of the kidney. There was a single ureteric orifice on the right side of the bladder. The fused kidney received its arterial supply from 2 vessels which arose from the right side of the aorta.

The adrenal glands were normally disposed, one on each side.

The other organs were small, in keeping with the stature of the patient. The aorta was diffusely hypoplastic but there was no coarctation.

No breast tissue was found beneath the nipples.

The report on the tissues submitted for histological examination (Dr. J. Suskin) read as follows:

The lung shows an organizing bronchopneumonic consolidation. The pituitary and adrenal glands show some autolytic changes. The liver appears normal. The skin is chromatin-positive, over 50% of the prickle cells showing sex chromatin. The uterus shows the presence of endometrium.

The ovary appears to have a cortex of ovarian stroma only and a hilum of tortuous vessels and epithelial-like cells which could possibly be collections of the Leydig type of cell found in the hilar regions of normal ovaries.

COMMENT

This case, though chromatin-positive, showed the classical features of Turner's syndrome in addition to the renal abnormality. Other interesting features were the history of menstruation and the previous admission to hospital for swelling of the knees and ankles. This illness may have been the acropathy which has been described in cases of gonadal dysgenesis. The lack of resistance to the pneumonic infection was presumably unrelated to the congenital abnormalities.

Most cases of gonadal dysgenesis appear to be genetically determined. It has been suggested that other cases may be caused by a deleterious influence which adversely affects the embryo. The renal abnormality in this case would be compatible with such a concept. Both the renal abnormality and the gonadal dysgenesis might have their origin in a disturbance of ontogenetic events which occur about the 7th and 8th weeks of intrauterine life. Though reduplicated, fused or double kidney is a relatively common abnormality, its association with contralateral renal agenesis is distinctly rare. Campbell[3] reported the occurrence of 342 cases of double kidney in 51,880 autopsies. In only 2 of these was the opposite kidney absent. In Grumbach's series of 22 cases of gonadal dysgenesis[1] one patient had a reduplicated ureter. A horseshoe kidney was one of the many congenital anomalies recorded by Chokas[4] in a patient with gonadal dysgenesis. This coincidence of renal and gonadal defects indicates the necessity for investigation of the urinary system in these cases.

The unexplained hypertension which has been described in association with gonadal dysgensis might be a manifestation of undetected renal abnormalities.

SUMMARY

A case is reported in which chromatin-positive gonadal dysgenesis was associated with Turner's syndrome and a fused right kidney with left renal agenesis.

We thank the Medical Superintendent, Dr. T. M. Adnams, for permission to submit this report for publication.

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NOTES AND NEWS : BERIGTE

UNIVERSITEIT VAN PRETORIA

FAKULTEIT GENEESKUNDE

Die Universiteit is voornemens om in 1961 'n *voltydse* kursus wat oor een akademiese jaar strek, vir die Diploma in Volksgesondheid aan te bied.

Aansoeke om toelating tot die kursus moet aan die Registrateur, Universiteit van Pretoria, Pretoria, gerig word en hom vóór 31 Desember 1960 bereik.

* * *

LEISURE READING FOR THE DOCTOR

Some recent publications are of particular interest to medical practitioners, who may while away a few interesting hours with these books during the coming holiday season.

1. **The Life of Sir Alexander Fleming,*** by André Maurois, the well-known, distinguished and elegant biographer. M. Maurois delves fully into all the scientific detail of Fleming's experiments, recounting setbacks as well as successes. His light and deft touch provides an extraordinarily readable account of the fascinating history of penicillin and its discoverer. The following quotation from Balzac fittingly heads the *Epilogue*:

'Only in extraordinary circumstances does the name of a scientist reach out beyond the borderline of science and take its place in the annals of humanity.'

2. **The Triumph of Surgery,*** by Jürgen Thorwald, the author of *The Century of the Surgeon.* This volume takes up the history of surgery after the discovery of local anaesthesia had made possible many new advances in the treatment of disease. Names that high-light the pages include the Mayo Brothers, Charcot, Freud, Macewen, Hughlings Jackson, Gowers, Bassini, Kocher, Sims, Mikulicz, Sauerbruch. These indicate the interesting historical scope of the volume.

3. **Mostly Murder,*** by Sir Sydney Smith.

This is an autobiography by the doyen of Forensic Pathologists, who was recently honoured by New York University during the Second International Meeting on Forensic Pathology and Medicine. Sir Sydney's characteristically modest account of his life and his career embraces some of the most satisfying problems to whet the appetite of the medical reader.

Many of his famous exploits in the forensic realm have become classics of medical reconstruction.

This delightful volume combines instruction with entertainment as few books have done.

* * *

COLLEGE OF PHYSICIANS, SURGEONS AND GYNAECOLOGISTS OF SOUTH AFRICA

Mr. J. Douglas, M.D., F.R.C.S., of Johannesburg, has been elected President of the College in succession to Prof. G. A. Elliott, who occupied the post for the first 4 years of the life of the College.

* Obtainable from Juta & Co., Ltd., Johannesburg and Cape Town.

THE WELLCOME TRUST NEW MEMBER

Prof. John McMichael, M.D., F.R.C.P., F.R.S., who holds the Chair of Medicine in the University of London at the Postgraduate Medical School, Hammersmith, has been appointed a Trustee of the Wellcome Trust in place of Sir Henry Dale, *O.M., C.B.E.,* F.R.C.P. F.R.S., who retired from the Trusteeship in July 1960, and was succeeded as Chairman by the Rt. Hon. the Lord Piercy, *C.B.E.* Professor McMichael's appointment became effective on 10 October 1960.

Sir Henry Dale will continue to serve the Trust in an advisory capacity as scientific consultant.

* * *

LARGE-SCALE CANCER DRUG STUDY PLANNED FOR AFRICA

A large-scale study to test the effectiveness of a new method of administering Methotrexate (which has been shown to shrink certain types of malignant tumours) is planned in Kenya, East Africa. The research study will be financed by the African Research Foundation and the Sloan-Kettering Institute of New York. A team of scientists led by Dr. R. Sullivan has been laying the foundations for the study since early this year.

According to reports received in New York, Dr. Michael Wood, a British plastic surgeon, stated in Nairobi that the drug has saved a number of patients who had been considered too far advanced for surgical treatment. The greatest effectiveness, he said, was in cancer of the cervix, nasal sinuses and face.

To date, all trials of this drug have been on patients who have not responded to any other treatment, e.g. radiotherapy or surgery. Tests indicate that the drug is not effective in cancer of the liver.

The new treatment consists of administering Methotrexate continuously through an intra-arterial catheter. At the same time intramuscular injections are given to reduce the toxic effects of the Methotrexate. This technique was developed by Dr. Wood and Dr. John Duff, of Nairobi's King George VI Hospital.

In successful cases the treated tumours were all said to have regressed. In cervical cancer, large, craggy growths have disappeared completely in about 10 days, according to Dr. Wood.

'We are of course following up the cases which have been treated successfully because we would not like to say yet that this is a cure,' Dr. Wood stated.

'The drug obviously has great potentialities now that we know what type of drug has this effect, and the chemists who are working on it may be able to get a more selective drug.'

Patients are being taken from many parts of East Africa to two hospitals in Nairobi, where the programme will be carried out.

Methotrexate is one of a group of anti-cancer drugs developed by Cyanamid International's Lederle Laboratories, in Pearl River, New York, in a $6 million research programme that has been under way since 1939. It has undergone clinical testing in the U.S.A., and in other parts of the world.

INTERNATIONAL CONFERENCE ON ANTICOAGULANTS

Dr. M. M. Suzman, of Johannesburg, recently attended this Conference in London, where he read a paper on *An Evaluation of the Effect of Long-Term Anticoagulant Therapy on the Prognosis of Coronary Artery Disease.*

The Conference is under the Chairmanship of Sir George Pickering and is sponsored by Evans Medical Ltd.

Dr. Suzman has also been invited to lecture on problems of anticoagulant therapy at the Edinburgh Royal Infirmary and some of the London hospitals.

The following is a list of the papers to be read at the Conference in London:

FIRST DAY

A review of the Action of Oral Anticoagulants on the Blood Coagulation Mechanism: *Prof. Hunter.*

The Liver in Relation to Anticoagulant Therapy: *Prof. Sherlock.*

The Place of the Quick's One Stage Test: *Prof. de Nicola.*

Laboratory Control of Anticoagulant Therapy: *Prof. Owren.*

Experiences with Thrombotest: *Dr. W. Walker.*

The Problems Associated with Laboratory Control: *Dr. R. Biggs.*

Treatment from the Pathologists point of view: *Dr. R. Aidin.*

General discussion on the interpretation and expression of laboratory results.

Experience with Fibrinolysin in the Treatment of Thrombo-embolic Disease: *Prof. Koller.*

Selection of Patients for Life-Long Anticoagulant Therapy: Organization of Therapy of large groups of Patients: *Prof. Owren.*

DISCUSSION

SECOND DAY

Acute Coronary Insufficiency: *Dr. P. Wood.*

Long-term Therapy in Coronary Thrombosis: *Dr. A. S. Douglas.*

An Evaluation of the Effect of Long-term Anticoagulant Therapy on the Prognosis of Coronary Artery Disease: *Dr. M. M. Suzman.*

DISCUSSION

Anticoagulant in Peripheral Vascular Disease: *Dr. R. L. Richards.*

Problems Associated with Long-Term Anticoagulant Therapy: *Dr. J. L. Stafford.*

Problems relating to Long-Term Therapy in Australia: *Sir L. Marrow.*

DISCUSSION

The G.P. Role in Anticoagulant Therapy: *Dr. Petrie.*

Anticoagulant Prophylaxis against Venous Thrombosis and Pulmonary Embolism in Injured Patients: *Dr. Sevitt.*

Anticoagulants in Cerebral Thrombosis: *Dr. Millikan* and *Dr. Marshall.*

DISCUSSION

Pulmonary hypertension and mitral Valvular disease in relation to Anticoagulants: *Dr. R. Emmanuel.*

Panel Discussion (1 hour): Professor Pickering—*Chairman;* Professor P. A. Owren, Dr. P. Wood, Dr. Millikan, Professor Hunter.

AN EVALUATION OF THE EFFECT OF LONG-TERM ANTICOAGULANT THERAPY ON THE PROGNOSIS OF CORONARY ARTERY DISEASE*

In the present report, the prophylactic value of long-term anticoagulant therapy is assessed by comparing the fatality rates in 779 survivors of acute myocardial infarction maintained on continuous long-term anticoagulant therapy with the rates observed in 1,111 survivors whose treatment with anticoagulants was limited to the acute phase of the presenting attack of infarction. Separate consideration is given to 291 patients who discontinued their long-term anticoagulant treatment after varying periods. Following recovery from the presenting attack of infarction, the entire series of 2,181 traced survivors, drawn from both hospital and private practice, were followed parallel in time till death or to the end of the present study (30 June 1960) for periods ranging from 12 to 150 months. An additional 222 patients were lost to follow-up and 50 were partly traced. Separate comparisons are made in relation to age and sex, in respect of the previous incidence of angina and infarction and according to whether the patient received hospital or private treatment.

The results show that in the group of long-term treated patients, observed for 2,579 patient-years and in whom previous infarction was a feature in 38% of the cases, there were 172 deaths giving a total fatality rate of 22%, whereas in the short-term treated group of patients observed for 4,262 patient-years and in whom only 17% had had previous infarction, the deaths numbered 600, a total fatality rate of 54%.

In the group that discontinued long-term anticoagulant therapy, 35% of the patients died during a total period of 713 patient-years. The duration of anticoagulant treatment prior to its discontinuation did not appear to influence the subsequent mortality and the majority of deaths occurred within the first 2 years.

Significant differences in mortality were observed between the long- and short-term treated patients in all ages, but within each group there were more deaths in patients over the age of 60 years.

A comparison of the annual fatality rates in all treated and untreated patients exposed to risk shows a significant difference in favour of those receiving long-term therapy, the mean rates being 5.6% and 12.3% and the 5-year survival rates 74% and 53% respectively. Within each group there were more deaths in each year amongst the patients who had experienced one or more episodes of infarction prior to the presenting attack, but these differences are substantially greater in those who were not receiving long-term anticoagulant treatment.

Since anticoagulant therapy maintained without interruption favourably influences the prognosis in survivors of myocardial infarction and is distinctly more effective when instituted after the first episode than after a recurrent one, this form of treatment can be expected to be of value when instituted early in the course of coronary atherosclerosis before the patient has suffered the impact of the first infarction. Its use, therefore, is indicated as a prophylactic measure in patients with angina pectoris as well as in certain cases of atypical and asymptomatic coronary artery disease.

* Synopsis of a paper read by Dr. M. M. Suzman, M.D., F.R.C.P. (*Johannesburg*) at the International Conference on Anticoagulants held in London in November 1960, with Sir George Pickering in the Chair.

HEALTH SERVICES IN BRITAIN

The Reference Division of the Central Office of Information of the United Kingdom Government Overseas Information Services London, has issued a revised edition (March 1960) of the publication entitled *Health Services in Britain*. This is an up-to-date account covering:

1. Public Health.
2. The National Health Service.
3. The School Health Service.
4. Industrial Health.
5. Health Services in Scotland.
6. Health Services in Northern Ireland.
7. Medical Research.
8. Professional Qualifications and Training.

A list of *Appendixes* concludes this useful reference manual which can be obtained from Her Majesty's Stationery Office, London.

* * *

PHYSIOLOGY OF REPRODUCTION

PRELIMINARY ANNOUNCEMENT OF A TRAINING PROGRAMME

In recognition of the world-wide need for scientific training in reproductive physiology, the Worcester Foundation for Experimental Biology plans to initiate on 1 January 1961, a postdoctoral program in this field under a grant from the Population Council.

Fellowships for the program will be awarded to candidates possessing the Ph.D., M.D. or their equivalents. These Fellowships will carry a stipend of $5,500 per annum and will be for a twelve month period. An allotment will also be made for round-trip travel to Shrewsbury, Massachusetts. Application blanks may be secured from the Research Director of the Worcester Foundation for Experimental Biology, and should be returned at an early date. They will be processed by a selection committee of experts, and the Fellowship awards for the first year will be announced late in 1960. Applicants for participation in the program in 1962 and later years may communicate with the Director at any time, but their applications will not be acted upon in 1960.

The program will consist of a course of lectures and laboratory work. During the latter part of the year each Fellow will have the opportunity to participate in a research project pertinent to his interests and within the capacity of the program.

The lecture series will be given by the Program Director, various members of the staff of the Worcester Foundation, and guest experts. The lectures and accompanying laboratory work will cover various phases of reproductive processes, particularly in mammals. Subjects to be treated will involve a review of reproductive processes in the male, including consideration of spermatogenesis, hormonogenesis, the control of testis function, and the functional endocrinology of testis hormones. Extensive attention will be given to oogenesis, ovulation and fertilization in the female, factors affecting the entire course of pregnancy and embryonic development, as well as the postnatal physiology of the female. Additional topics will include the role of extra-reproductive tract organs in reproductive processes, genetic and nutritive factors in reproduction, and the control of fertility and sterility.

Laboratory exercises will include the study of characteristic reproductive phenomena in various species, analytic procedures employed in determining the chemistry of reproductive organs, the biochemistry of spermatozoa and ova, and hormone analyses pertinent to gonad function, to sex cycles, to gestation and lactation.

Further information from: The Worcester Foundation for Experimental Biology, 222 Maple Avenue, Shrewsbury, Massachusetts, U.S.A.

PREPARATIONS AND APPLIANCES

MEXAFORM

ANTIDIARRHOEAL AGENT

Ciba Ltd. announce the introduction of *Mexaform*.

Mexaform is a potent intestinal antiseptic containing *Vioform* and *Entobex*, two antibacterial and antiparasitic substances whose effects supplement and reinforce one another in ideal fashion. Vioform, a drug long acknowledged as an eminently dependable intestinal antiseptic, displays a broad range of antibacterial and antiparasitic activity. *Entobex* exerts a specific effect on pathogenic protozoa of various types (Amoeba, Giardia, Trichomonas, Chilomastix) and also possesses good antibacterial properties. *Mexaform* contains, in addition, *Antrenyl*, a spasmolytic which serves to combat the spasm, colic, and tenesmus frequently occurring in diseases associated with diarrhoea. *Mexaform* is excellently tolerated and can also be prescribed for children.

Indications: *Mexaform* is indicated for all types of diarrhoea, including especially diarrhoea of infectious origin due to bacteria or protozoa, as well as unspecific diarrhoea or diarrhoea of uncertain aetiology and summer diarrhoea. *Mexaform* may be employed both in the acute stage of the disease and in chronic or relapsing cases.

Administration and Dosage: The average dosage for adults is 1 tablet of *Mexaform* three times daily; in severe cases, treatment can be initiated with 2 tablets three times daily. Children should be given 1 tablet of *Mexaform* one to three times daily, depending on the child's age. A few days' treatment is generally sufficient.

In areas in which amoebiasis is common, it is advisable to continue the treatment for one week, even where pathogens can no longer be traced in the stools and where a symptomatic improvement or clinical recovery has already been achieved.

REDUCE BOXING INJURIES

WITH VARIDASE TABLETS

Tests conducted over a period of 9 months have shown that amateur boxers given a tablet of *Varidase* suffer less bruising and cutting than boxers who receive no pre-fight treatment.

A total of 494 young boxers was involved in the test, conducted by Dr. Joseph L. Blonstein, honorary medical officer of the British Amateur Boxing Association. Half received *Varidase* about an hour before the contest, half received 2 dummy tablets of identical taste and appearance. There was

a 50% reduction of general bruising and an 11% reduction of haematomata (including 'black eyes') in those who received *Varidase* as compared to those who did not.

Dr. Blonstein added that when *Varidase* was given after bouts to boxers with injuries, the tablets helped the rapid elimination of bruising, haematomata and injured tissues. Those who received this treatment were able to resume boxing 1–2 weeks sooner than injured boxers who were given only the usual first aid.

The tablets did not act as a stimulant or a sedative. The reaction to treatment was solely due to the promotion of quicker healing.

Varidase was administered by placing the tablets in the buccal sulcus, where they were allowed to dissolve slowly to permit maximum absorption. If the tablets are swallowed, their beneficial effect is inactivated by gastric juice.

Developed in the Lederle Laboratories of Cyanamid International, *Varidase* has been widely used by physicians to assist wound healing, to clear up pockets of infection in the body, and to treat infected burns and gangrenous and ulcerative conditions. In certain cases, the drug is administered topically to the wound or injected intramuscularly, as well as given by mouth.

Varidase contains 2 enzymes (streptokinase and streptodornase) which act to break down diseased tissue in the body and permit freer access to therapy and quicker healing.

Lederle Laboratories Division of the American Cyanamid Company, P.O. Box 4461, Johannesburg. *Telephone*: 835-8081.

NIVAQUINE: 200 MG. TABLETS

Maybaker (S.A.) (Pty.) Ltd. announce the availability of 200 mg. tablets *Nivaquine* brand chloroquine sulphate in containers of 100 tablets, in addition to containers of 10 and 500 tablets. Each tablet contains the equivalent of 150 mg. chloroquine base.

ROVAMYCIN CAPSULES

Maybaker (S.A.) (Pty.) Ltd. wish to announce that when their present stocks of *Rovamycin* tablets are exhausted they will be replaced by *Rovamycin* capsules in the same strength and container sizes, i.e. 20 × 250 mg. spiramycin and 100 × 250 mg. spiramycin.

Details about *Rovamycin* may be obtained from the company's Medical Department, P.O. Box 1130, Port Elizabeth.

ANATENSOL

SQUIBB FLUPHENAZINE DIHYDROCHLORIDE

Synthesis of a new orally administered drug that relieves anxiety and tension without clouding consciousness has been announced by Squibb International of Olin Mathieson Chemical Corporation.

Development of this phenothiazine derivative *Anatensol* (known generically as fluphenazine) by The Squibb Institute for Medical Research, culminates extensive research for a tranquillizer suitable for the treatment of symptoms of anxiety and tension, commonly seen by the general practitioner, particularly in ambulant patients.

Chemical Structure: It is designated as 4-{3-[(2-trifluoromethyl)-10-phenothiazinyl] propyl}-1-piperazineëthanol. *Anatensol* has been tested by clinical investigators in the form of the dihydrochloride.

Mental Alertness Maintained: *Anatensol* lessens anxiety and tension but seldom impairs mental alertness and acuity when used at the recommended dosage. It 'mitigates apathy, indifference, inertia and anxiety-induced fatigue' and 'increases efficiency by facilitating psychic relaxation.'

Action: Site and mode of action have not been determined. Its pharmacological actions are tranquillizing and antiemetic.

Indications: *Anatensol* is effective in anxiety and tension, both in the ambulatory and the bed patient. It has proved effective in disabling anxiety and tension states manifested by such symptoms as apprehension, restlessness, irritability, insomnia, nausea and vomiting where no organic disease was evident and in anxiety and tension associated with somatic conditions such as hypertension and cardiovascular disease.

Administration: Oral.

Side Effects: In the recommended daily dosage *Anatensol* has rarely produced undesirable side effects.

Contraindications and Precautions: Because of its potentiating effect, *Anatensol* should not be used in patients given large doses of hypnotics or in severely depressed patients. As with other phenothiazine drugs, it should be administered with caution to patients with a history of convulsive disorders. It should also be used with care when dosages exceeding the recommended ones are employed.

Dosage: In anxiety and tension, the recommended dose for adults is 1 mg. daily. If necessary, the total daily dose may be increased to 1 mg. *b.i.d.* or two 1 mg. tablets given as a single dose in patients with relatively severe symptoms who have tried the lower dosage. A daily dose in excess of 2 mg. should be used with caution.

Supply: Tablets of 1 mg. in bottles of 25's.

Further information may be obtained from Squibb Laboratories (Pty.) Ltd., P.O. Box 9975, Johannesburg.

KENACOMB OINTMENT

Since Triamcinolone Acetonide, a potent new corticosteroid for topical dermatological use, was developed by the Squibb Institute for Medical Research, Squibb Laboratories have made available to South Africa a number of useful dermatologic preparations.

The first presentation to arrive in South Africa in April 1959 was *Kenacort-A* Ointment (Squibb Triamcinolone Acetonide), especially intended for inflammatory, pruritic and allergic skin conditions when bacterial superinfection is not a problem.

In the same month a *Kenacort-A* preparation with protection against bacterial superinfection became available. This is *Kenacort-A* with *Graneodin Lotion*. *Graneodin* (Squibb neomycin-gramicidin) is effective for the treatment and prevention of many superficial bacterial infections of the skin. *Kenacort-A* with *Graneodin Lotion* is especially suited to wet, weeping lesions. For dry, scaly skin conditions, *Kenacort-A* with *Graneodin Ointment* was introduced in December 1959.

In April 1960 *Kenacort-A* with *Graneodin Ophthalmic Ointment* was made available offering prompt, gratifying, usually prolonged relief of inflamed, itching and burning eye conditions.

Squibb Laboratories are now adding a new, even more useful preparation to the already established *Kenacort-A* family of products. This preparation is marketed under the trade name *Kenacomb Ointment*. Each gramme of *Kenacomb Ointment* supplies:

Triamcinolone acetonide	1.0 mg.
Neomycin base (as sulphate) ...	2.5 mg.
Gramicidin	0.25 mg.
Nystatin	100,000 units.

Kenacomb Ointment exerts 5 distinct therapeutic actions in one preparation: anti-inflammatory, antipruritic, anti-allergic, antibacterial and anti-fungal. It is especially formulated to prevent or combat bacterial or monilial infection in cutaneous disorders. Topically applied, *Kenacomb* controls and induces a rapid clearance of burning and itching inflamed skin lesions—and provides safe local antibacterial and antimonilial protection particularly for conditions such as pruritus ani and vulvae and diaper rash which are representative examples where bacteria and monilia cause or contribute to the disease.

Supplies of *Kenacomb Ointment* in 5 mg. tubes are now fully available in South Africa.

Squibb Laboratories (Pty.) Limited, P.O. Box 9975, Johannesburg.

MELLERIL

Sandoz Ltd., Basle, Switzerland announce the introduction of *Melleril*.

Composition: 10 mg., 25 mg. and 100 mg. tablets of thioridazine HCl, Sandoz.

Action and Uses: *Melleril* has a specific action on certain brain sites, in contrast to the more 'diffuse' action of other phenothiazines. This is evidenced by minimal anti-emetic effect, and minimal extrapyramidal stimulation. *Melleril* has less 'spill-over' action to other brain areas; hence the virtual elimination of undue sedation, drowsiness or autonomic nervous system disturbance.

Melleril has virtual freedom from such toxic effects as jaundice, Parkinsonism, skin photosensitivity, skin eruption, disturbed body temperature regulation, blood dyscrasias, etc. All these properties add up to improved tranquillization with a greater margin of safety in general office practice, in ambulatory psychiatric outpatient clinics, and in hospitalized patients.

Melleril has value in the following indications:

Mental and emotional disturbances in the office, anxiety, apprehension and tension states, acute and chronic psychoneuroses.

Mental and emotional disturbances in the hospital, pre- and post-operative apprehension and agitation.

Severe psychoneuroses, agitated psychoses.

Behaviour problems in children.

Agitated geriatric patients.

Intractable pain.

Alcoholism.

Administration and Dosage: Usual starting dose in non-psychotic patients is 10 or 25 mg., 3 or 4 times a day. Psychotic patients require 100 mg. 3 or 4 times a day as a starting dose. Dosage must be individually adjusted until maximum therapeutic response is achieved.

Precaution: As with all synthetic drugs, regular blood counts are desirable during protracted treatment.

Contra-Indication: *Melleril* is contra-indicated in severely depressed or comatose states from any cause.

How Supplied:

Tablets 10 mg., 25's and 100's.

Tablets 25 mg., 50's, 200's and 1,000's.

Tablets 100 mg., 25's, 100's and 1,000's.

Further information, samples and literature may be obtained from Sandoz Pharmaceutical Department, P.O. Box 4461, Johannesburg.

Sole Distributors for South Africa: Alex. Lipworth Limited, P.O. Box 4461, Johannesburg.

MER-29

FOR INHIBITION OF CHOLESTEROL SYNTHESIS

Description: *Mer-29* is the Merrell brand name for triparanol, a new synthetic organic compound which is the first specific inhibitor of excessive cholesterol biosynthesis.

Pharmacology: Radioisotope studies in both animals and humans indicate that *Mer-29* directly inhibits cholesterol production in the liver, intestines and other tissues. This inhibitory action is partial, and occurs at the final stage of cholesterol biosynthesis.

Mer-29 produces substantial reductions in both serum and tissue cholesterol. The cholesterol: phospholipid ratio is significantly reduced and, in animals, studies indicate that *Mer-29* produced a fall in alpha- and beta-lipoprotein cholesterol, without affecting serum lipoproteins.

Advantages: *Mer-29* offers for the first time, a practical, safe and effective solution to the problem of hypercholesterolaemia.

Mer-29 is the only specific inhibitor of excessive cholesterol biosynthesis, reducing both serum and tissue cholesterol without dietary restrictions. In over 2,000 patients under clinical trial, elevated serum cholesterols were reduced in 85%–90% of cases. In general, the reduction was proportional to the pretreatment control levels, and the maximum fall was generally obtained after the 4th week of therapy. Increasing the daily dosage did not result in lower cholesterol levels. These findings indicate that *Mer-29* will not depress cholesterol levels below those necessary for normal metabolic needs.

Because *Mer-29* partially inhibits at the final stage of cholesterol biosynthesis—after formation of the steroid nucleus—it does not interfere with adrenal, endocrine and other vital metabolic functions.

Discussion: It has been shown that endogenous synthesis accounts for the main source (over two-thirds) of body cholesterol. Low-fat dietary restrictions are thus ineffective in preventing elevated serum cholesterol levels.

Mer-29 reduces endogenous cholesterol biosynthesis by 36%. This reduction occurs both in serum and tissues, because *Mer-29* has been shown to lower the total body miscible pool of cholesterol. The possibility of transferring cholesterol from serum to tissues is thus excluded.

Clinical Improvement: Preliminary findings indicate that after *Mer-29* therapy, both objective and subjective improvement has been reported in angina patients using the 'two-step' exercise tolerance test. It has been suggested that *Mer-29* may improve the adequacy of coronary circulation, and possibly also reduce the cholesterol content of human blood vessels, including coronary arteries. Investigations are proceeding.

Side Effects: Extensive, long-term trials have revealed no interference with normal liver and kidney functions, and no blood dyscrasias. Adrenal and endocrine functions are unaltered. Occasional mild gastro-intestinal upset and a skin rash have been reported. A false positive reaction for albuminuria occurred in a few cases.

Indications: Patients with hypercholesterolaemia; adjunctive therapy for conditions associated with abnormal cholesterol metabolism (coronary artery disease, generalized atherosclerosis, diabetes, cerebral arteriosclerosis).

Compatibility: *Mer-29* is compatible with anticoagulants, vasodilators and other drugs used in cardiovascular disease.

Caution: *Mer-29* should not be used during pregnancy.

Dosage: One 250 mg. tablet once a day before breakfast.

Supplied: Bottles of 30, light-yellow tablets of 250 mg.

Marketed in South Africa by Mer-National Laboratories (Pty.) Ltd., P.O. Box 6742, Johannesburg.

Distributed in South Africa by Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

COLIMYCIN ORAL SUSPENSION

M.L. Laboratories announce that Westdene Products (Pty) Ltd. have been appointed sole South African Distributors of *Colimycin* Oral Suspension, an effective concentrated diarrhoea product.

Colimycin contains 1 g. of neomycin, plus kaolin and pectin in balanced proportions per ounce of mixture in a pleasantly flavoured base. The wide antibacterial spectrum of neomycin makes *Colimycin* effective against almost all pathogens likely to be encountered in the gastro-intestinal tract. The addition of kaolin, an efficient adsorbent, assists materially in adsorbing bacteria and toxins in the bowel. Pectin, a purified carbohydrate, acts as an adsorbent and protects the bowel lining, while at the same time its decomposition products inhibit the growth of abnormal bacteria causing diarrhoea.

Colimycin concentrated suspension offers the following advantages:

1. Since most diarrhoeas are accompanied by nausea and vomiting, high concentration of medicament in small dosage is not only desirable but essential. (Each tablespoonful of *Colimycin* contains 0.5 g. of neomycin sulphate).

2. *Colimycin* offers effective and almost immediate control of diarrhoea, and consolidation of stools is usually accomplished within 24 hours of commencement of treatment; and

3. Because of its concentration and efficacy it has been found that therapy with *Colimycin* is economical since 2 fluid ounces or, at the most, 4 fluid ounces, is a complete course of treatment.

The advantage of a product that can offer effective and almost immediate control of diarrhoea even in infants is very important. Since control of diarrhoea is effected so rapidly side effects are unlikely to be encountered with *Colimycin*.

Recommended dosage is as follows:

Adults: 1 tablespoonful *stat.* 1 desertspoonful 4–6 times daily.

Children: 1 desertspoonful *stat.* 1 teaspoonful 4–6 times daily.

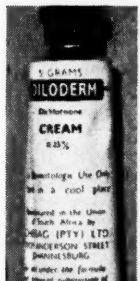
Infants: 1 teaspoonful *stat.* half teaspoonful 4–6 times daily.

Samples, information and literature available on request from Westdene Products (Pty) Ltd., P.O. Box 7710, Johannesburg.

DILODERM

SCHERING CORPORATION U.S.A.

Schering Corporation U.S.A. introduces the first chlorinated steroid, *Diloderm* (dichlorisone acetate) which was developed to provide superior topical steroid effectiveness. With *Diloderm*, anti-inflammatory activity is markedly enhanced at the local level without a corresponding increase in metabolic effects on systemic administration.



Totally different from all present steroids, *Diloderm* is chlorinated—the first such corticoid to be made available for clinical application. This unique structure may account for the unique specificity of *Diloderm* for topical use on the skin. *Diloderm* provides increased topical benefits in allergic, inflammatory and pruritic skin disorders responsive to topical steroid therapy including:

Atopic dermatitis;
Allergic dermatitis;
Infantile eczema;
Nummular eczema;
Eczematoid dermatitis;
Contact dermatitis;
Pruritus ani and vulvae;
Pruritus with lichenification;
Disseminated neurodermatitis.

Intramuscular administration of 25 to 80 mg. daily in humans confirms animal studies and demonstrates that *Diloderm* produces no changes in serum levels of sodium, phosphorus, calcium, magnesium, alkaline phosphatase or in circulating eosinophils, 17-ketosteroid excretion, potassium balance, nitrogen balance.

In contrast to the metabolic effects associated with other active anti-inflammatory steroids, the relative absence of such effects in therapy with *Diloderm* has been fufrther demonstrated by oral administra-

tion of *Diloderm* to patients undergoing therapy with conventional systemic steroids. In such cases, patients relapsed with oral dosages of *Diloderm* of 60, 80, 120 and 200 mg. daily. One patient, maintained on 10 mg. of prednisone daily, had a prompt relapse when given *Diloderm* in oral dosages of up to 240 mg. daily.

The general absence of absorption after topical application of *Diloderm* is evidenced by lack of systemic effect reported by investigators. In addition, eosinophil counts performed at 4 and 24 hours showed no significant change in subjects on whom 20 g. of *Diloderm* Cream was applied to the body and thoroughly massaged in.

Supplied:

Diloderm Cream 0.25%: 5 g. tube.
Neo-Diloderm Cream 0.25%: 5 g. tube.

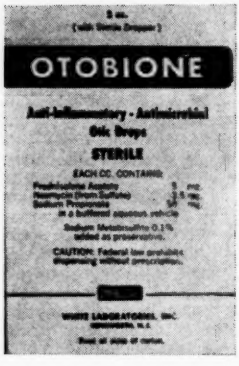
OTOBIONE

WHITE LABORATORIES INC.

Otobione is an anti-inflammatory and anti-microbial liquid intended for topical treatment of accessible ear infections.

Each c.c. contains:

Prednisolone Acetate	5 mg.
Neomycin (from sulphate) ...	3.5 mg.
Sodium Propionate	50 mg.



Otobione is buffered approximately to pH 6.2 to conform to that of the normal external ear canal. The formulation is designed to promote an optimal degree of local action with minimal distortion of otoscopic landmarks.

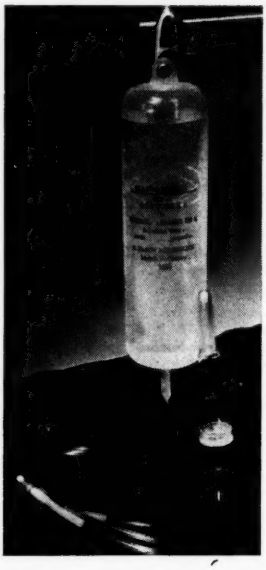
Otobione is indicated for topical treatment and symptomatic relief of external otitis and chronic otitis media due to susceptible organisms. Used prophylactically, *Otobione* also helps prevent infectious complications in allergic, seborrheic or neurogenic dermatoses of the external auditory canal.

Supplied: Bottles of 5 c.c. *sterile* ear solution with cellophane wrapped *sterile* dropper.

BRAUN PLASTIC INFUSION

A NEW DEVICE FOR THE STORAGE AND ADMINISTRATION OF INTRAVENOUS FLUIDS

The *Braun Plastic Infusor* is basically a large, disposable ampoule, made of polyethylene. Polyethylene is a light (S.G., 0.94), tough, transparent plastic which is neutral, insoluble in water and almost all other solvents. In moulding polyethylene it is not necessary to use any type of plasticizer or other chemical material; there is, therefore, no risk of chemical contamination of any kind. Polyethylene is completely impervious to moisture and gases. Control tests overseas and in South Africa indicate that the keeping qualities of intravenous fluids in *Braun Infusors* are at least as good as in the conventional glass bottles.



A 1,000 c.c. Infusor weighs (empty) less than 1/20 of the weight of a glass container of comparable size. It is virtually unbreakable, either with sudden blows or with sheer pressure. Freezing of the solution has no effect upon the Infusor, nor has sudden immersion in hot water. Administration of fluids is easy with the *Braun Infusor*, since no air inlet is required. The container merely collapses completely except for a residual 20–30 c.c., thus obviating all risk of an air embolism when a full 1,000 c.c. is discharged.

Braun Plastic Infusors are presently available in Normal Saline, Dextrose 5% in water, Dextrose 5% in Normal Saline, Ringer Lactate Solution and Darrows Solution (all 1,000 c.c.). Darrow's Solution is also available in 250 c.c. Infusors.

Most standard administration sets can be used with the Infusor, but *Intrafix*, another Braun product, is specially designed for use with the Infusor. *Intrafix* can also be used with standard glass containers, and is supplied sterile, and ready for use, in a clear plastic envelope.

Further information is available from:

Remedia (Pty.), Ltd., P.O. Box 151, Fordsburg, Johannesburg.

CENSEDAL: A DAYTIME SEDATIVE

Maybaker (S.A.) (Pty) Ltd. announce the introduction of *Censedal* brand allyl neopentyl barbituric acid.

Clinical studies have confirmed that *Censedal* is a useful daytime sedative, which, in therapeutic doses, seldom produces drowsiness. It is rapidly absorbed after oral administration and has a duration of action between that of amylobarbitone and that of phenobarbitone.

Censedal is indicated for sedation in anxiety, tension and phobic states and in senile agitation. It is not, however, effective against agitation or anxiety in psychotic patients and is not an effective anticonvulsant in epilepsy.

Censedal is presented as white scored tablets each containing 60 mg. (approx. gr. 1) and 200 mg. (approx. gr. 3) of the active compound.

Further particulars may be obtained from The Medical Department, Maybaker (S.A.) (Pty.) Ltd., P.O. Box 1130, Port Elizabeth.

(*Vervolg van bladsy 570b*)

MEDICAL PROCEEDINGS

MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

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Editor : Redakteur

H. A. Shapiro, B.A., Ph.D., M.B., Ch.B., F.R.S.S.Af.

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DIE MONDELINGE POLIO-ENTSTOFVELDTOG

Dit is diep te betreur dat die owerheid 'n veldtog van stapel gestuur het om lede van die publiek met 'n mondelinge polio-entstof te immuniseer voordat die mediese professie oor die implikasies van hierdie stap ingelig is, veral aangesien die betrokke prosedure nog nie in die Verenigde Koninkryk of die Verenigde State toegepas is nie. Wanneer 'n openbare bestuur 'n immunologiese avontuur van hierdie aard onderneem, behoort so 'n bestuur 'n baie duidelike besef te hê van die reperkussies van sy beleid en van die plig wat daar op hom rus om mediese praktisyns betyds in te lig oor die wetenskaplike implikasies van sy program. As dit nagelaat word, is mediese praktisyns nie in staat om konsekwente of selfs akkurate antwoorde te verskaf aan ouers wat hulle kom raadpleeg oor die wenslikheid daarvan om hul kinders met mondelinge entstof te laat behandel nie.

Die inligting wat die mediese professie ietwat laat bereik het, dui daarop dat:

i. Daar gedurende die oorgangstydperk met entstof van die Salk-tipe volgehou moet word.

ii. Die mondelinge entstof geneem moet word as 'n toevoegsel tot die Salk-entstof.

iii. Slegs verswakte entstof van tipe 1 in die eerste plaas beskikbaar gestel is omdat die meeste van ons epidemies deur tipe 1 veroorsaak word; dit beklemtoon dus die noodsaaklikheid om beskerming voorlopig met die Salk-entstof in stand te hou.

iv. Die mondelinge entstof sonder enige gevaar geneem kan word as ander inspuitings toegedien is.

v. Die tweede en derde mondelinge dosisse wat in 1961 toegedien sal word, al 3 tipes sal bevat en nie tipe 2 en tipe 3 onderskeidelik nie.

vi. Kinders wat aan koors ly nie die entstof behoort te neem nie.

vii. Die entstof met veiligheid aan swanger vrouens gegee kan word.

viii. Dit nog nie moontlik is om die entstof tot beskikking van private praktisyns te stel nie, maar dat dit gedoen sal word as die organisasiemoeilikhede uit die weg geruim nie.

Ons wil egter beklemtoon dat daar sekere groepe is wat spesiaal aan gevaar blootgestel is, nl. pasiënte wat met steroïede behandel word, en dié wat onlangs 'n operasie ondergaan of aan ander spanningstoestande onderwerp was.

Die Suid-Afrikaanse entstof bevat klein hoeveelhede penisillien en streptomisien. Kinders wat allergies vir mondelinge penisillien is, behoort waarskynlik nie met die mondelinge entstof behandel te word nie.

Dit skyn ook dat die oorspronklike plan prakties is om pasgeborenes met die entstof te behandel en alle babetjies dus onvatbaar te maak.

Trouens, sommige gesaghebbendes beskou die immunisasie van alle kinders tussen die ouderdom van 3 en 6 maande as noodsaaklik; anders sal dit nooit moontlik wees om 'n onvatbare gemeenskap te produseer nie, met al die daaruitvoortspruitende (moontlik rampspoedige) gevare wat die onbeskermdes sal bedreig as gevolg van blootstelling aan kwaadaardige wilde virussoorte.

In Israel het die insluiting van kinders tussen 3–6 maande oud in die immunisasieveldtog geen moeilikheid opgelewer nie.

Die welslae van die veldtog hang af van die toediening van die entstof aan al die lede van die bevolking wat aan gevaar blootgestel is. Dit is 'n belangrike oorweging wat die veiligheid van die prosedure betref, want die mondelinge entstof word saam met die ontlasting afgeskei, en die virussoorte kry dus 'n kans om te versprei.

Geen wetenskaplike bewys van die immunologiese doeltreffendheid van die Suid-Afrikaanse entstof is tot beskikking van die mediese professie gestel nie. Dit is bv. wenslik om te weet watter teenstof-reaksie plaasvind wanneer die entstof gegee word aan drievoudig-negatiewe pasiënte, d.w.s. persone in wie se sera daar geen teenstowwe vir die 3 soorte poliovirus voorkom nie; ons weet ook nie hoe lank die teenstowwe wat deur die lewende entstof geproduseer kan word, aktief sal bly nie. Die beskikbare getuienis het slegs op kort tydperke betrekking.

Teelock[1] het onlangs verslag gedoen oor 'n poliomiëlitis-epidemie in Mauritius waar entstof van die Koprowski-Sabin-tipe (berei in Suid-Afrika) aan die bevolking gegee is, maar eers nadat die uitbreking feitlik tot 'n einde gekom het. In Mauritius het daar vier gevalle van poliomiëlitis voorgekom ná die toediening van hierdie Suid-Afrikaanse entstof. In 2 gevalle was die kinders (hulle was albei 3 jaar oud) reeds voor die inenting siek. In die ander 2 gevalle was daar geen geskiedenis van siekte voor inenting nie, maar die entstof is toegedien slegs 13 dae voordat die pasiënte siek geword het.

Daar is getuienis dat die virussoorte vryelik onder die lede van 'n huishouding of die inwoners van 'n geslote inrigting, bv. 'n weeshuis, versprei, maar verspreiding tussen families kom nie gereeld voor nie. Dit is derhalwe waarskynlik dat iedere persoon wat beskerming teen poliomiëlitis met die mondelinge entstof verlang die lewende entstof persoonlik sal moet inneem.

Dit is onwenslik om die verswakte soorte gedurende die somermaande toe te dien, soos vandeesjaar gedoen is, omdat die vestiging van die poliovirus in die spysverteringskanaal waarskynlik deur die aanwesigheid van ander virusse belemmer sal word.

As doeltreffende stappe gedoen is om 'n wetenskaplike verklaring aan alle mediese praktisyns te stuur, sou 'n doeltreffend ingeligte professie in staat gewees het om met die openbare owerheid saam te werk.

Dit is die tweede keer dat 'n anti-polio-immunisasieveldtog in hierdie land van stapel gestuur word sonder dat doeltreffende inligting vooraf tot beskikking van die mediese professie gestel word. In 1955, by geleentheid van die Salk-entstofveldtog, het ons daarvoor gesorg[2] dat die professie, vir die eerste keer in Suid-Afrika, die basiese inligting kry wat nodig was om ons kollegas in staat te stel om tot 'n beslissing oor die entstof te geraak. By hierdie jongste geleentheid moes die professie hom weer eens verlaat om die inligting wat in die leke-pers gepubliseer is—'n onbevredigende, onwenslike en ondoeltreffende manier om 'n professionele groep oor 'n tegniese aangeleentheid in te lig.

Die memorandums wat tot beskikking van die mediese pers en die mediese professie gestel is, het verskyn eers nadat die veldtog feitlik voltooi was en met net 'n geringe mate van welslae bekroon is.

Dit skyn asof daar doeltreffende immunisasie van skoolkinders was, maar die resultate met voor-skoolse kinders was teleurstellend. 'n Baie groot gedeelte van hierdie kinders kon bereik gewees het in die geregistreerde kleuterskole waar hulle 'n geskikte gevange bevolking vorm. In enige veldtog moet daar ook rekening gehou word met onvermydelike afwesigheid op enige besondere dag—'n toestand wat maklik die hoof gebied kan word deur die eenvoudige plan om die betrokke kinders in die daaropvolgende week van die veldtog te immuniseer.

Watter dringendheid daar ook al bestaan het vir 'n onderneming soos die polio-entstofveldtog (en ons het reeds aangedui dat die raadsaamheid daarvan op hierdie tydstip van die jaar twyfelagtig is) is dit besonder ongelukkig dat geen voorafgaande stappe gedoen is om die mediese professie betyds in te lig voordat die veldtog van stapel gestuur is nie.

Daar word derhalwe aangedring by die owerhede wat verantwoordelikheid vir 'n anti-polio-immunisasieveldtog aanvaar om die mediese professie op 'n doeltreffende wyse en betyds oor alle wetenskaplike aspekte van die veldtog in te lig voordat 'n begin daarmee gemaak word. Op hierdie manier sal dit moontlik wees om iedere praktisyn te oorreed om aktief deel te neem aan die verspreiding van propaganda onder die publiek, sonder wie se heelhartige steun en samewerking so 'n skema nooit kan slaag nie.

1. Teelock, B. (1960): Brit. Med. J., **2**, 1272.

2. Redaksioneel (1955): Mediese Bydraes, **1**, 129.

FLAGYL

A NEW TRICHOMONAL AGENT

Maybaker (S.A.) (Pty) Ltd. announce the introduction of a new antitrichomonal agent, *Flagyl* brand metronidazole.

Flagyl represents an important advance in the treatment of *Trichomonas vaginalis* infections in females and males since it provides, for the first time, effective and well-tolerated systemic therapy. The simple regime of treatment (one tablet by mouth 3 times daily for 7 days) has been found adequate even in many long-standing vaginal infections.

Flagyl tablets are available in a prescriber unit of 21 x 200 mg. tablets.

REVIEWS OF BOOKS

BONE X-RAY DIAGNOSIS

Principles of Bone X-Ray Diagnosis. George Simon, M.D., M.R.C.P., F.F.R. (1960. Pp. 169 + Index. With 244 Figs. 66s. 3d. plus 1s. 9d. delivery charge). London and Durban: Butterworth & Co. (Publishers) Ltd.

In this book Dr. Simon has attempted to expound the principles of X-ray diagnosis in relation to bone pathology by commencing with the main presenting radiographic feature and proceeding to a differential diagnosis.

From the systematic viewpoint he has not been entirely successful in this attempt, but he has produced a good practical guide to bone radiology, and one that is easy to read and to understand.

It is sufficiently elementary to have a place in every student's and doctor's library, and it is so well illustrated that it deserves a place in the radiologist's library as well.

The illustrations are beautifully clear, and the text is concise and informative.

This book can be recommended to all doctors with any interest in bone pathology.

EPILEPSY

Neurochemistry of Epilepsy. By Donald B. Tower, M.D., Ph.D. (1960. Pp. 282 + Index. With 29 Figs. 72s.). Oxford: Blackwell Scientific Publications Ltd.

In 6 well-written chapters Professor Tower traces the two principal areas of neuronal metabolism which have been implicated as associated with the seizure process, viz. the metabolism of glutamic acid and alpha-aminobutyric acid on the one hand, and acetylcholine and electrolyte metabolism on the other. The former is related to the sphere of oxidative metabolism and energy sources, while the latter is more directly concerned with membrane excitability and the functional activity of neurones.

In the process of achieving this object, the author presents a lucid and engaging account of carbohydrate, amino acid and electrolyte metabolism covering many aspects of nervous system function, as a basis for the discussion of epileptogenic states. At the same time he marshalls all the *in vivo* and *in vitro* experimental data in relation to each aspect of the study.

While in general he succeeds in combining the clinician's interest with the searching struggle of the neurochemist and the physiologist, there are sections which the neurologist will find too technical. At no stage, however, does this interfere with the appreciation of the gist of the argument, which includes a chapter on the modes of action of various anticonvulsants and an appraisal of their value in the understanding of seizure mechanisms.

In the concluding chapter, having summarized the final common mechanisms which generate seizures, he hastens to add:

'This picture gives no indication of the nature of the derangements which underlie these final mechanisms.'

Various theories are then discussed and the points at which further investigation to improve our knowledge could profitably be undertaken, are indicated.

The real value of this book to the clinician, however, is in the neat, careful organization of the neurochemical processes characterizing normal neuronal activity and seizure states which Professor Tower has assembled with such clarity in one volume.

GENERAL ANAESTHESIA

General Anaesthesia. Volume 1: *Basic Principles;* Volume 2: *Techniques, Special Fields and Hazards.* Edit. by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A. and Cecil Gray, M.D., F.F.A.R.C.S., D.A. (1959. Pp. 531 + Index. With 121 Figs. 161s. Postage 2s.). London and Durban: Butterworth & Co. (Publishers) Ltd.

This comprehensive survey of the principles and practice of anaesthesia falls into two parts and appropriately into two separate volumes.

The first volume deals with *Basic Principles* and the second volume is devoted to techniques, anaesthesia in special fields as well as the hazards associated with the practice of this branch of medicine. This volume includes a final and excellent chapter (pp. 423–431) on the medico-legal aspects of general anaesthesia.

Volume 1 (*The Basic Principles*) opens with a concise account of the history of anaesthesia, the remaining chapters being devoted to anatomy and physiology, with particular emphasis on the physiology of the nervous and the cardiovascular systems. Separate chapters are devoted to the clinical assessment of the patient before anaesthesia and there is a special chapter dealing with the methods of investigation of pulmonary functions, premedication and basal narcosis (rectal). The pharmacology of volatile anaesthetics and intravenous anaesthesia are both dealt with in individual chapters which precede the chapter on the signs of anaesthesia. The principles of muscular relaxation and the relaxants themselves receive special treatment. The volume concludes with a survey of water and electrolyte balance, blood transfusions, reactions to trauma and the principles of anaesthetic apparatus.

This catalogue of topics is a sufficient indication of the comprehensive way in which the basic prin-

ciples of anaesthesia have been covered by a panel of distinguished authors. South African readers will be particularly interested in the fact that a former South African (Prof. David Slome) is the author of the chapter entitled the *Physiology of Respiration* (pp. 53–106).

Volume 2 is devoted to specific practical problems and includes special studies of controlled hypotension, hypothermia and artificial respiration. Anaesthesia in the surgical specialities is dealt with chapter by chapter in respect of each special field.

Paediatrics and geriatrics receive separate consideration, as do certain medical areas of practice, e.g. diabetes. A particularly useful chapter, is that dealing with *The Difficult Patient*. It is also useful to have gathered together in a convenient compass (pp. 400–410) the information devoted to the *Principles and Practice of Oxygen Therapy*.

The different subjects have been dealt with by eminent and expert authorities on the various anaesthetic aspects. This has led to considerable variety in the method of presentation of the material and some overlapping—not necessarily a fault.

The 2-volume survey has taken adequate account of the rapidly expanding fields in the modern practice of anaesthesia and is pre-eminently suitable for the post-graduate student preparing for his higher qualification in anaesthetics. It will also be invaluable as a source of reference for the already established anaesthetist.

INFECTIOUS DISEASES

Communicable and Infectious Diseases. By Frankling H. Top, A.B., M.D., M.P.H., F.A.C.P., F.A.A.P., F.A.P.H. (1960. Pp. 812 and illustrations. £5 14s. 9d.). St. Louis: The C. V. Mosby Company.

This is a new and fourth edition of a well-known text on infectious diseases. It is lavishly illustrated and includes 15 excellent colour plates.

Section 1 is devoted to general considerations. Section 2 deals with infectious diseases classified according to the portal of entry. The text is remarkably comprehensive and is clearly based on the vast practical experience of the Editor and his 22 contributors.

In discussing the prevention of poliomyelitis, the authors endrose the value of the Salk vaccine and point out that, with the use of live virus vaccines, although there is the danger of a return to virulence, so far no harmful effects have been seen in several hundred individuals observed over several years (page 72). Since this edition was published, the final decision to permit the use of attenuated live virus vaccine has amply endorsed the accuracy of this view.

In the chapter on rubella the authors take a conservative view about the risk of congenital defects occurring in the offspring of pregnant mothers who become infected during the early stages of their pregnancy. As they point out on page 462, the following congenital abnormalities have been attributed to maternal rubella in early pregnancy viz.:

'Heart disease, unilateral and bilateral cataracts, deaf-mutism, mental retardation or deficiency, microcephaly, multiple anomalies, and a few others less commonly noted. Many others have reported similar defects, but there is uncertainty about the proportion of infants so affected. It is still too early to assess fully the implications of these findings. Further investigations are necessary, for the study has been approached retrospectively and from the wrong end, namely, the affected infant. The proper approach is to make a prospective study of the universe of pregnant women, dividing them into the two groups of those who did and those who did not contract German measles during pregnancy and then noting the incidence of congenital abnormalities in the offspring of both groups for differences which could be considered significant. Others concur in this view. This would be a tedious and difficult task, as German measles is very poorly reported and cases usually do not come to the attention of a physician. In spite of the difficulty, prospective studies are under way. In the reported studies, German measles is assumed to have occurred in many instances, on the statement of the family. There are many German measles-like rashes.'

This scientific assessment of the situation should be of great assistance to the practitioner, who is often in the difficult position of having to advise pregnant women about the risks to the foetus in cases of infection with rubella.

In dealing with the vexed problem of viral hepatitis, the authors draw attention to the recent demonstration of asymptomatic blood carriers, without a history of previous infection with jaundice. This is extremely important in connexion with the transmission of the disease.

At present there is no satisfactory method of eliminating the virus from whole blood or its products other than albumin and gamma globulin. There is certainly no justification for using pooled plasma, and the facilities of a modern, scientifically directed transfusion service should find no practical problem in preparing plasma in single units, thus reducing the risk of infection by this means to the same low chance that exists with the use of a single blood transfusion.

As far as sterilization of instruments is concerned, it is clear that simple rinsing and immersion in liquid disinfectants are not reliable. Adequate sterilization must require not only thorough cleansing but also prolonged boiling or autoclaving. There is much to be said for regarding the syringe needle as an expendable item which should be used only once.

The volume is a mine of clinical information and will be of great interest and value to the paediatrician as well as the general practioner and the specialist physician.

OTOLARYNGOLOGY

Textbook of Otolaryngology By David D. DeWeese, M.D. and William H. Saunders, M.D. (1960. Pp. 464, 354 illustrations. $8.75). St. Louis: The C. V. Mosby Company.

Professors DeWeese and Saunders are to be congratulated on their work in producing what will probably become a popular standard textbook.

It is a splendid production, beautifully prepared and printed, and is a delight to read. With few exceptions the 354 illustrations are well chosen and clearly emphasize the points in the text. Exceptionally good are those relating to technique in clinical examination of the E.N.T. case.

The basic sciences of anatomy and physiology are adequately and clearly put forward.

The content has much to commend it, as it includes the 'forgotten subjects,' e.g. the salivary glands, cysts and tumours of the neck, speech disorders, rehabilitation of the deaf. Special emphasis is given to diseases of the facial nerve.

The chapters on *Vertigo* and *Tinnitus* are very clear and comprehensive and this is necessary in two such subjects, which are perplexing to the student.

Diseases and physiology of the ear are completely up to date.

The new concepts of middle ear deafness, and the 5 types of tympanoplastic procedures, and the variations and modifications of the stapes mobilization operation are clearly outlined.

Speech Disorders by DeWeese and Herold Lillywhite is a valuable inclusion, indicating in detail what speech development is to be expected in each year of the growing child. It emphasizes the importance of early diagnosis of deafness in young children.

In dealing with rehabilitation of the deaf, the reader is given practical information on hearing aids, group instruction and audiometry.

The classification of vertigo is complete, though formidable to the student.

Useful details are given in the management of epistaxis, while the management of infections of the paranasal sinuses represents sound clinical practice.

ANAEROBIC BACTERIOLOGY

Anaerobic Bacteriology in Clinical Medicine. A. Trevor Willis, Ph.D. (Leeds), M.B., B.S. (Melb.). (1960. Pp. 163 + Index. With 13 Figs. 34s. 6d. plus 1s. 3d. delivery charge). London and Durban: Butterworth & Co. (Publishers) Ltd.

This easily read, well documented book can be thoroughly recommended to clinical pathologists, teachers and post-graduate students. The worker in the field of anaerobic bacteriology will welcome it because, although he will be familiar with some of the methods and procedures described, he will have at his disposal, in small compass, a great deal of valuable information culled from a very extensive literature.

The 6 chapters deal with methods of cultivation, examination and identification, characteristics, infections and toxicology. Pathogenic and non-pathogenic clostridia, anaerobic cocci and fusiform bacilli are discussed fully.

Surface cultivation, particularly on half-antitoxin lactose-egg-yolk-milk agar, in a McIntosh and Fildes anaerobic jar, would appear to be the author's favourite method of isolation and identification. Isolation by a 'shake' method in deep agar is mentioned but without elaboration. This was used successfully and almost to the exclusion of all others by workers of earlier days and is still common in France. Possibly, it produces the best anaerobic conditions of all procedures, is cheap and demands no special apparatus. It may be the only way of separating, e.g. *Clostridium botulinum*, Type D from *Cl. sporogenes* or *Cl. tetanomorphum*.

The use of the guinea-pig in separating a pathogenic, from a non-pathogenic, anaerobe is not mentioned. The inoculation of an animal with a mixture of *Cl. septicum* and *Cl. sporogenes* plus, possibly, an 'activator' like calcium chloride or adrenaline may permit the isolation, in pure culture, of the pathogen from the heart blood or liver of the cadaver.

The author rightly says that a subculture of the growing edge (whisker) of a tetanus surface culture may give a pure culture but does not note that the bacteria in such an isolation may be non-toxigenic.

Few workers in the veterinary anaerobic field would link *Cl. chauvaei* and *Cl. septicum* so closely as the author does. *Cl. chauvaei* is, culturally, much more fastidious than *Cl. septicum* and is, *for practical purposes*, non-toxigenic whereas *Cl. septicum* produces a potent and easily demonstrable toxin.

On p. 121, it is stated that *Cl. botulinum* toxin 'is destroyed in a few minutes by boiling'; on p. 141 '*Cl. botulinum* species are characterized by the production of highly potent heat-stable exotoxins' and (in the same paragraph) 'It (toxin) is destroyed by boiling'. Possibly 'heat-stable' is a misprint for 'heat-labile'.

It is possibly a pity that the author has given another meaning (p. 135) to the letters 'M.R.D.' which, to older workers, meant 'minimum reacting dose' and referred to the smallest amount of a toxin that would cause a reaction when injected intracutaneously into an animal. For Dr. Ellis the letters stand for 'minimum reactive dose' which he defines as the smallest amount of toxin that produces some indicating effect. An M.R.D. is, according to the author, equivalent to '1 unit of toxin'. The word 'unit' should preferably be confined to antitoxin; if it must be used for toxin, it would prevent confusion if it were prefixed by some symbol such as Lf or L+.

Although these few criticisms occupy a large portion of the review, they must not be taken as a reflection of the reviewer's opinion of the book as a whole. It will find a place not on the shelves but on or near the work bench of every laboratory that has to deal with the isolation and identification of anaerobic bacteria.

There are 315 references to the literature.

BLOOD TECHNIQUES

Handbook of Haematological and Blood Transfusion Technique. By J. W. Delaney, F.I.M.L.T. (1960. Pp. 295 + Index. With 45 Figs. and 3 Plates. 51s. 9d. plus 2s. delivery charges).
London and Durban: Butterworth & Co. (Publishers) Ltd.

This book has obviously been written by a very experienced teacher and laboratory worker. It is clear and concise and contains a minimum of theoretical discussion. This is most suitable, since it is only concerned with methodology and is intended for the training of technicians and for use as a laboratory manual. Many books do exist for these purposes, but the present one has achieved a high standard.

It covers a wide scope. There are short but adequately detailed descriptions of almost every routine haematological and blood transfusion technique one may need at present. It also includes several that are very highly specialized, e.g. vitamin B_{12} assay, AHG assay and biological tests for pyrogens. A few of the chapters are discursive only, e.g. the first, which deals with the origin, life and death of the blood cells, whereas the majority begin with a short general discussion after which details of the appropriate techniques are presented.

The chapters on haematology cover haemoglobinometry, blood cell counting, red cell indices, investigation of anaemic and polycythaemic states, the haemolytic anaemias, haemorrhagic and purpuric states. The section on blood transfusion includes chapters on blood group antigens and antibodies, the various blood group systems and general aspects of transfusion work. There is a chapter on the use of radioisotopes and a few pages on the use of statistics. The bibliography is short but the index is complete.

With any book of methods it is probably inevitable that some of the procedures recommended by the author will be unacceptable to some readers. In this book, however, the instances are few and they hardly detract from its merit. To those who are responsible for the training of technicians in these subjects, it will be most useful and convenient.

The book is well bound and the printing, colour plates, line drawings and photomicrographs of high quality.

CORRESPONDENCE

INTERNAL FIXATION OF FRACTURES BY MEANS OF POLYURETHANE FOAM

To the Editor: In March of this year your *Journal* published a preliminary report by the writer on the use of *Polyurethane Foam in the Treatment of Fractures*.

A review of all the cases treated at the Ernest Oppenheimer Hospital, has revealed a high incidence of relatively late complications (6 to 12 weeks).

In view of the fact that the cause of such complications has not yet been ascertained, it has been decided to discontinue the use of Polyurethane Foam in fresh fractures, pending further studies.

E. M. McLean

The Ernest Oppenheimer Hospital,
Welkom.

MGA POST-GRADUATE REFRESHER COURSE

To the Editor: The closing date for the forthcoming Post-Graduate Course arranged by the Medical Graduates Association, together with the Faculty of Medicine of the University of the Witwatersrand, to be held from 16 to 21 January 1961, is 15 December.

Members who intend applying for the course are requested to do so well before this date, to ensure a place on the course.

J. Teeger,
President.

Medical Graduates Association,
University of the Witwatersrand,
Medical School,
Hospital Street,
Johannesburg.
Telephone: 44-7040.

NEED FOR DERMATOLOGISTS

To the Editor: May I be allowed to use your columns to issue an appeal? I would like to ask those colleagues, including interns, who wish to become dermatologists please to get in touch with me.

Year by year this country has stood in an increasing need for young specialists with a modern training in dermatology. Considerable opportunities exist for them, and will continue to exist for some time to come. In a survey published by the Department of Education, we were surprised and pleased to see that at least 26 South African practitioners wished to become dermatologists. We would be glad to hear from them and from any others with similar aspirations.

Those who are undecided are particularly welcome to approach me, in case we can help them. The Dermatologists' Group regards it as important if some worthy colleagues can be added eventually to their number by informing and encouraging them.

G. H. Findlay,
(*President: Dermatological Group*,
Medical Association of South Africa).

528 Medical Centre,
Pretorius Street,
Pretoria.

MEDICAL PRACTICE AND THE HIPPOCRATIC DUTY

To the Editor: One of my patients has just related to me an event in a hospital casualty department which was the absolute negation of the humanitarianism which is supposed to distinguish the practice of medicine. It never reached the newspapers and it strikes me that there must be a thousand such cases for every one that is published.

The following lines may be useful to hospital Superintendents. I do not reserve the copyright.

INSTRUCTIONS TO CASUALTY OFFICERS

The Law is more important than the Patient,
Do not ignore that element'ry fact.
At present, with Barbarity renascent,
You must never, ever disregard *The Act*.

When a mother brings her baby, torn and bleeding,
Fighting for each tiny, gasping breath,
Take no notice of her sentimental pleading
That her Little Treasure's on the brink of death.

Fill the Forms and see you make her sign them
(Hands red-wet with oozing infant blood),
Pin the copies carefully, align them;
Make quite sure they're fully understood.

Obey *The Rules* in every little item,
(To be humane is only fit for mutts).
Vicious rules! I know you'd like to slight 'em,
I'm sure you won't—*you haven't got the guts*.

H. J. Leviseur, M.R.C.S., L.R.C.P.

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